Part III

# White Cell Disorders

## WORD KEY

**Cervical** • Relating to the neck

**Inguinal** • Relating to the groin area

**Subclavian** • Situated beneath the clavicle or collarbone

**Thoracic** • Relating to the chest

**Humoral** • When relating to immunity it means antibody formation

**Thymus** • Ductless gland located above the heart that plays a role in immunity

**Albinism** • Partial or total absence of pigment in the hair, skin, and eyes

**Convalescence** • Period of recovery after a disease or surgery

**Photophobia** • Unusual intolerance of light

**Prognostic** • Prediction of the chance for recovery

**Pyknosis** • Shrinkage of cells through degeneration

**Rhinorrhea** • Excessive watery discharge from nose

**Sepsis** • Systemic inflammatory response to infection that includes symptoms such as fever, hypothermia, tachycardia, and others

**Auer rods** • Elliptical, spindle-like inclusions composed of fused azurophilic granules that may be present in myeloblasts, monoblasts, or promyelocytes in the various AMLs

**Cytochemistry** • Special stains usually performed on bone marrow samples that are examined microscopically to identify enzymes, lipids, or other chemical constituents within the blast population of cells in acute leukemia

**Dyspnea** • Shortness of breath

**Dysplasia** • Abnormal maturation of cells in the bone marrow

**Gingival hyperplasia** • Swelling of the gingival tissues (gums); in leukemia, this is due to infiltration of the gum tissues with leukemic cells

**Immunophenotyping** • Process of using monoclonal antibodies directed against cell surface markers to identify antigens unique to the specific lineage and stage of maturation

**Lineage** • Referring to one specific cell line

**Lymphoma** • Neoplasm involving abnormal proliferation of cells arising in the lymph nodes; these tumor cells may also metastasize to involve extranodal sites

**Meningeal leukemia** • Leukemic cells proliferating in the central nervous system

**Myelodysplasia** • Abnormal maturation and/or differentiation of granulocytes, erythrocytes, monocytes, and platelets

**Oncogene** • Gene that is responsible for the development of cancer

## WORD KEY

**Clonal** • Disease arising from a single cell

**Deep vein thrombosis** • Formation of a blood clot in the deep veins of the legs, arms, pelvis, etc.

**Myelofibrosis** • Increase in the reticulin or fibrotic tissue in the bone marrow.

**Myeloproliferative** • Disease that results in the uncontrolled overproduction of normal-appearing cells in the absence of an appropriate stimulus

**Organomegaly** • Enlargement of the organs

**Osteosclerosis** • Abnormal increase in the thickening or density of bone

**Plethora** • Excess blood volume

**Pruritus** • Itching

**Therapeutic phlebotomy** • Withdrawing blood for a medical purpose

**Transient ischemic attack** • Neurological defect, having a vascular cause, producing stroke symptoms that resolve in 24 hours

**Trisomy** • In genetics, having three homologous chromosomes instead of two

**Alkylating agent** • Agent that introduced an alkyl radical into the compound in place of a hydrogen atom; these agents interfere with cell metabolism and growth

**Angiogenesis** • Development of blood vessels

**Organomegaly** • Enlargement of any organ

**Refractory** • Resistant to ordinary treatment

**Autoimmune hemolytic anemia** • Process by which cells fail to recognize self and consequently make antibodies that destroy selected red cells

**Direct antiglobulin test** • Laboratory test for the presence of complement or antibodies bound to a patient's red blood cells

**Erythroderma** • Abnormal widespread redness and scaling of the skin, sometimes involving the entire body

**Monosomy** • Condition of having only one of a pair of chromosomes, as in Turner's syndrome, where there is only one X chromosome instead of two

**Pathognomonic** • Indicative of the disease

**Raynaud's phenomenon** • Intermittent attacks of pallor or cyanosis of the small arteries and arterioles of the fingers as a result of inadequate arterial blood supply

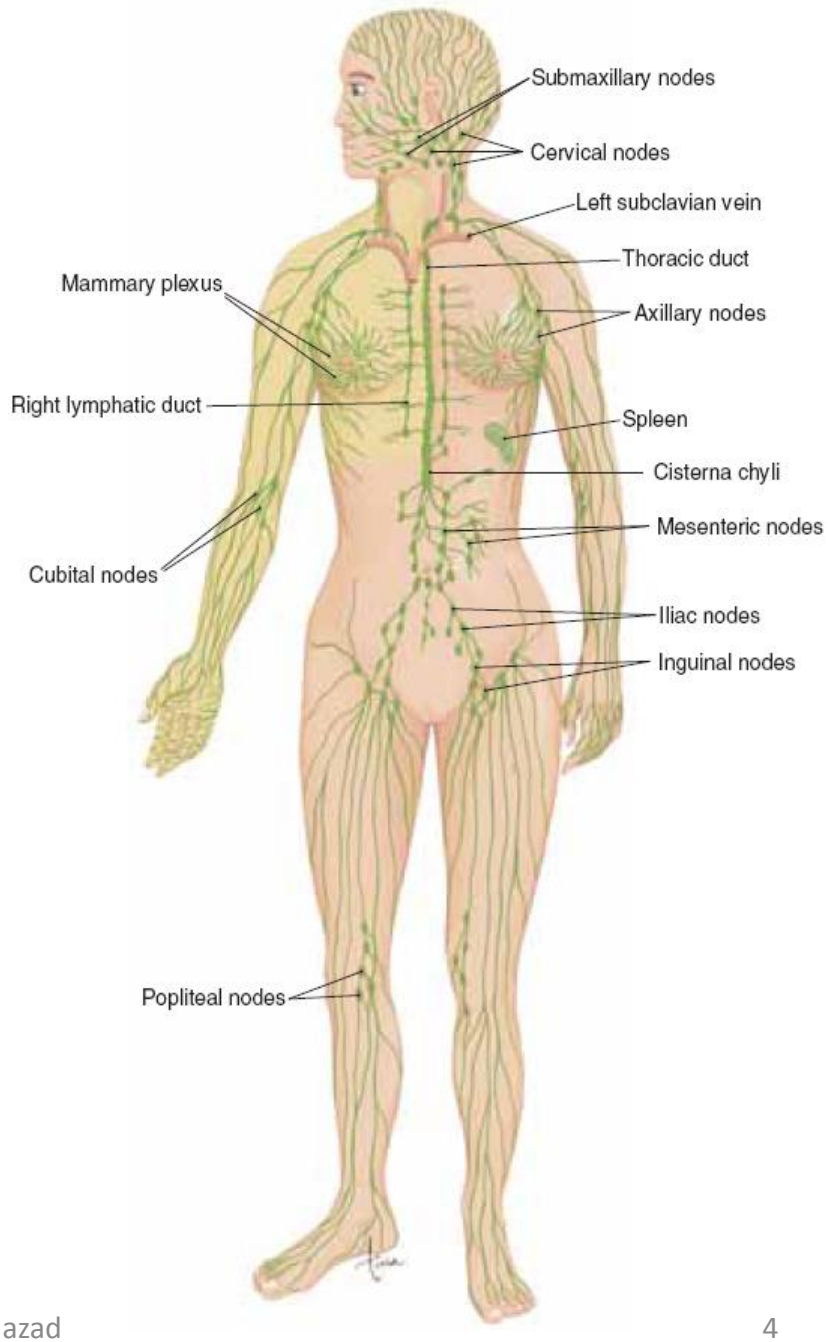
**Plasmapheresis** • Plasma exchange therapy, involving the removal of plasma from the cellular material that is then returned to the patient

**Rouleaux** • Group of red cells stuck together that look like a stack of coins

**Translocations** • Alteration of a chromosome through the transfer of a portion of it either to another chromosome or to another portion of the same chromosome

## Table 10.1 White Cell Terminology

- **Neutrophilia** Increase in segmented neutrophils
- **Leukocytosis** Increase in white cells
- **Left shift** Increase in bands and metamyelocytes in the peripheral smear; seen in response to infection
- **Leukemoid reaction** Exaggerated response to infection; resulting in high white count and increased numbers of metamyelocytes, bands, and possibly younger cells
- **Leukoerythroblastic picture** Immature white cells, immature red cells, and platelet abnormalities seen in the peripheral smear



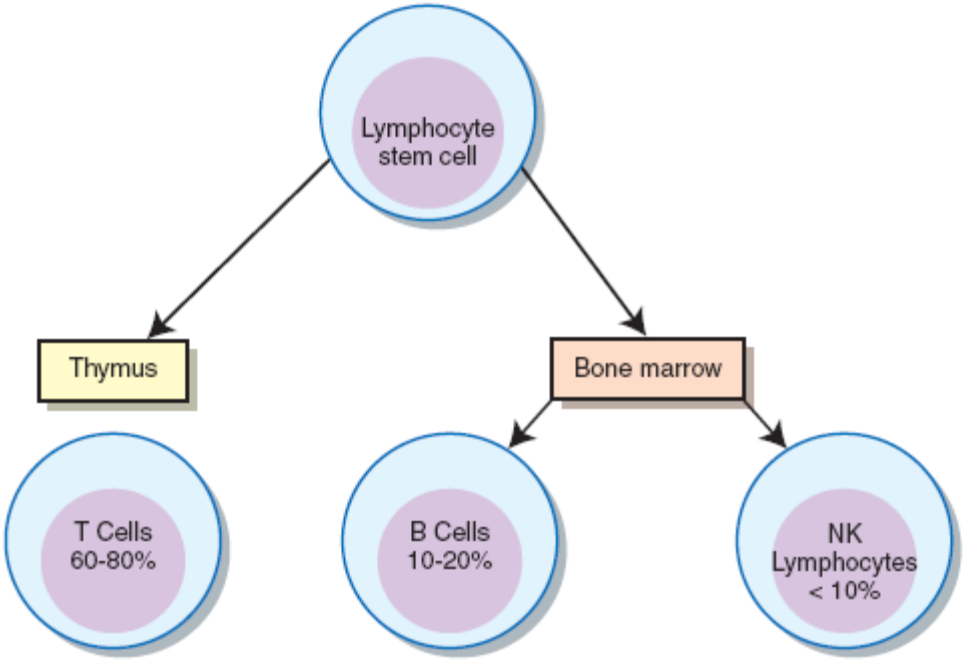



**Figure 9.13** Subpopulations of lymphocytes.

**Table 9.3 Manual Differential Reference Ranges for Adults and Infants**

| | Adults | Up to 1 Year |
|---|---|---|
| Segmented neutrophils | 50% to 70% | 20% to 44% |
| Bands | 2% to 6% | 0% to 5% |
| Lymphocytes | 20% to 44% | 48% to 78% |
| Monocytes | 2% to 9% | 2% to 11% |
| Eosinophils | 0% to 4% | 1% to 4% |
| Basophils | 0% to 2% | 0% to 2% |

**Table 9.2 Leukocyte Counts at Different Ages***

| Age | Leukocyte Count |
|---|---|
| Birth | 4 to 40 |
| 4 Years | 5 to 15 |
| Adult | 4 to 11 |

*All values $\times 10^9$/L.

Table 32-2 Key Causes of Neutrophilia

**Acute inflammatory** — collagen vascular, vasculitis
**Acute infectious** — bacterial, some viral, fungal, parasitic
**Drugs, toxins, metabolic** — corticosteroids, growth factors, uremia, ketoacidosis
**Tissue necrosis** — burns, trauma, MI, RBC hemolysis
**Physiologic** — stress, exercise, smoking pregnancy
**Neoplastic** — carcinomas, sarcomas, myeloproliferative disorders

Table 32-3 Key Causes of Neutropenia (brief partial list)

**Drugs** — cancer chemotherapy, chloramphenicol, sulfas/other antibiotics, phenothiazines, benzodiazepine, antithyroids, anticonvulsants, quinine, quinidine, indometacin, procainamide, thiazides
**Radiation**
**Toxins** — alcohol, benzene compounds
**Intrinsic defects** — Fanconi's, Kostmann's, cyclic neutropenia, Chédiak–Higashi
**Immune-mediated** — collagen vascular disorders, RA, AIDS
**Hematologic** — megaloblastic anemia, myelodysplasia, marrow failure, marrow replacement
**Infectious** — any overwhelming infection
**Others** — starvation, hypersplenism

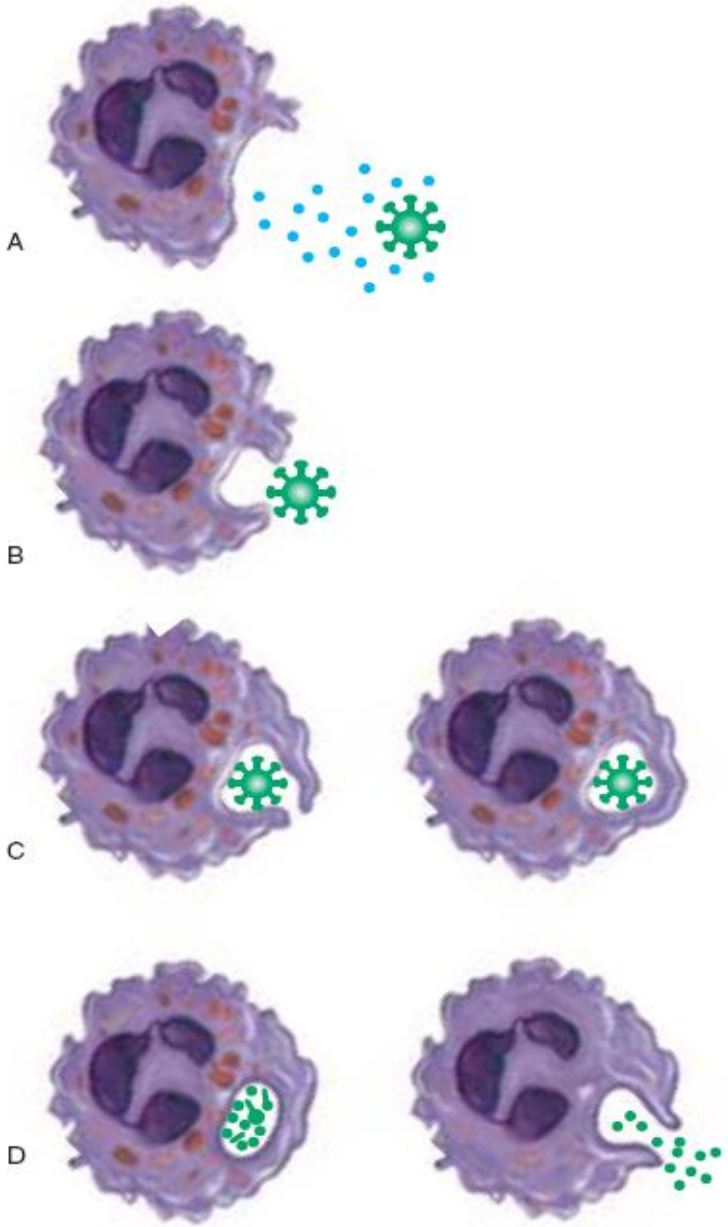



**Figure 10.1** Mechanism of phagocytosis. Stages depicted are (*A*) chemotaxis and directed motility, (*B*) opsonization, (*C*) ingestion, (*D*) degranulation and digestion.

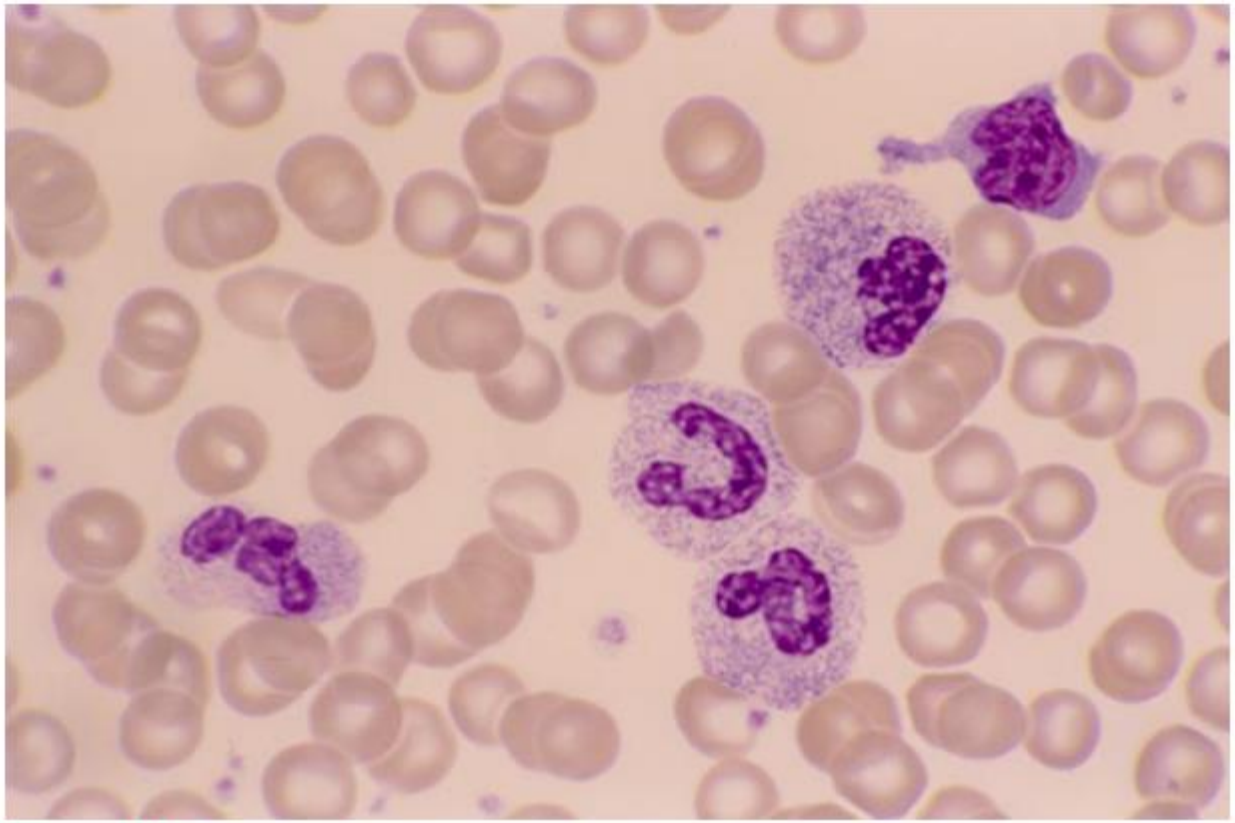


**Figure 10–1 Neutrophilia.** The neutrophils show heavy granular staining ("toxic granulation").

## Table 32–5 Key Causes of Eosinophilia

**Allergic** — urticaria, hay fever, asthma
**Inflammatory** — eosinophilic fasciitis, Churg–Strauss syndrome
**Parasitic** — trichinosis, filariasis, schistosomiasis
**Nonparasitic infections** — systemic fungal, scarlet fever, chlamydial pneumonia of infancy
**Respiratory** — pulmonary eosinophilic syndromes (Loeffler's, tropical pulmonary eosinophilia), Churg–Strauss syndrome
**Neoplastic** — CML, Hodgkin lymphoma, T cell lymphomas
**Idiopathic hypereosinophilic syndromes** — affecting heart, liver, spleen, CNS, other organs
**Others** — certain drugs, hematologic and visceral malignancies, GI inflammatory diseases, sarcoidosis, Wiskott–Aldrich

## Table 32–6 Key Causes of Basophilia

**Myeloproliferative disease**
**Allergic** — food, drugs, foreign proteins
**Infectious** — variola, varicella
**Chronic hemolytic anemia** — especially post-splenectomy
**Inflammatory** — collagen vascular diseases, ulcerative colitis

## Table 32–7 Key Causes of Monocytosis

**Infectious** — tuberculosis, subacute bacterial endocarditis, syphilis, protozoan, rickettsial
**Recovery from neutropenia**
**Hematologic** — leukemias, myeloproliferative disorders, lymphomas, multiple myeloma
**Inflammatory** — collagen vascular diseases, chronic ulcerative colitis, sprue, myositis, polyarteritis, temporal arteritis
**Others** — solid tumors, immune thrombocytopenic purpura, sarcoidosis

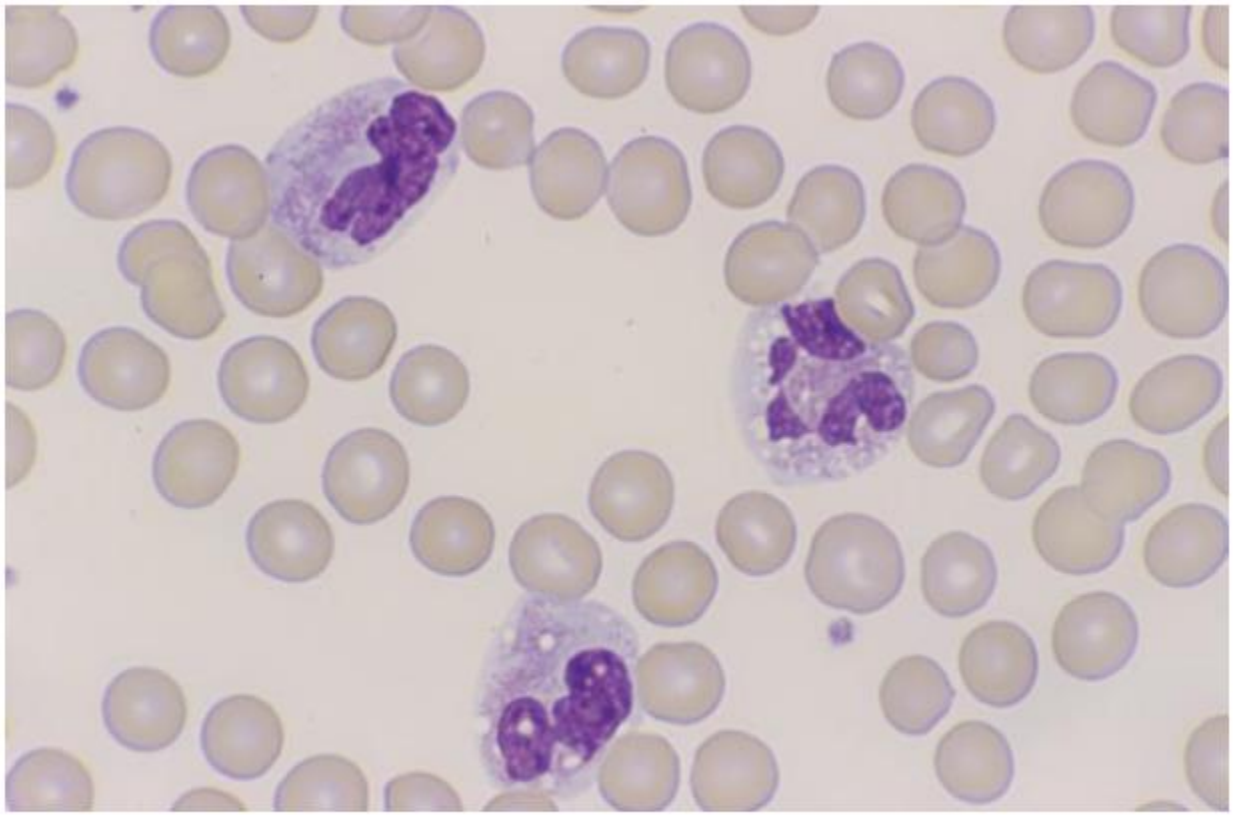


**Figure 10–2 Eosinophilia.** All three leukocytes in the field are eosinophils. The eosinophil count was 14,000 μL. The patient developed endomyocardial fibrosis. No cause was established.

Table 32–8 Key Causes of Lymphocytosis

**Infectious** — many viral, pertussis, tuberculosis, toxoplasmosis, rickettsial
**Chronic inflammatory** — ulcerative colitis, Crohn's
**Immune mediated** — drug sensitivity, vasculitis, graft rejection, Graves', Sjögren's
**Hematologic** — ALL, CLL, lymphoma
**Stress** — acute, transient

Table 32–10 Key Causes of Lymphopenia

**Destructive** — radiation, chemotherapy, corticosteroids
**Debilitative** — starvation, aplastic anemia, terminal cancer, collagen vascular disease, renal failure
**Infectious** — viral hepatitis, influenza, typhoid fever, TB
**AIDS associated** — HIV cytopathic effect, nutritional imbalance, drug effect
**Congenital immunodeficiency** — Wiskott–Aldrich
***Abnormal lymphatic circulation*** — intestinal lymphangiectasia, obstruction, thoracic duct drainage/rupture, CHF

Table 32–11 Key Causes of Plasmacytosis

**Viral** — infectious mononucleosis, measles, rubella, HIV
**Bacterial** — tuberculosis, syphilis, streptococcus, staphylococcus
**Parasitic** — malaria, trichinosis
**Inflammatory** — SLE, RA, inflammatory bowel disease, alcoholic liver disease
**Neoplastic** — plasma cell leukemia, myeloma, CLL
**Immune stimulation** — immune complex disease (serum sickness), drug sensitivity, transfusion
**Trauma**

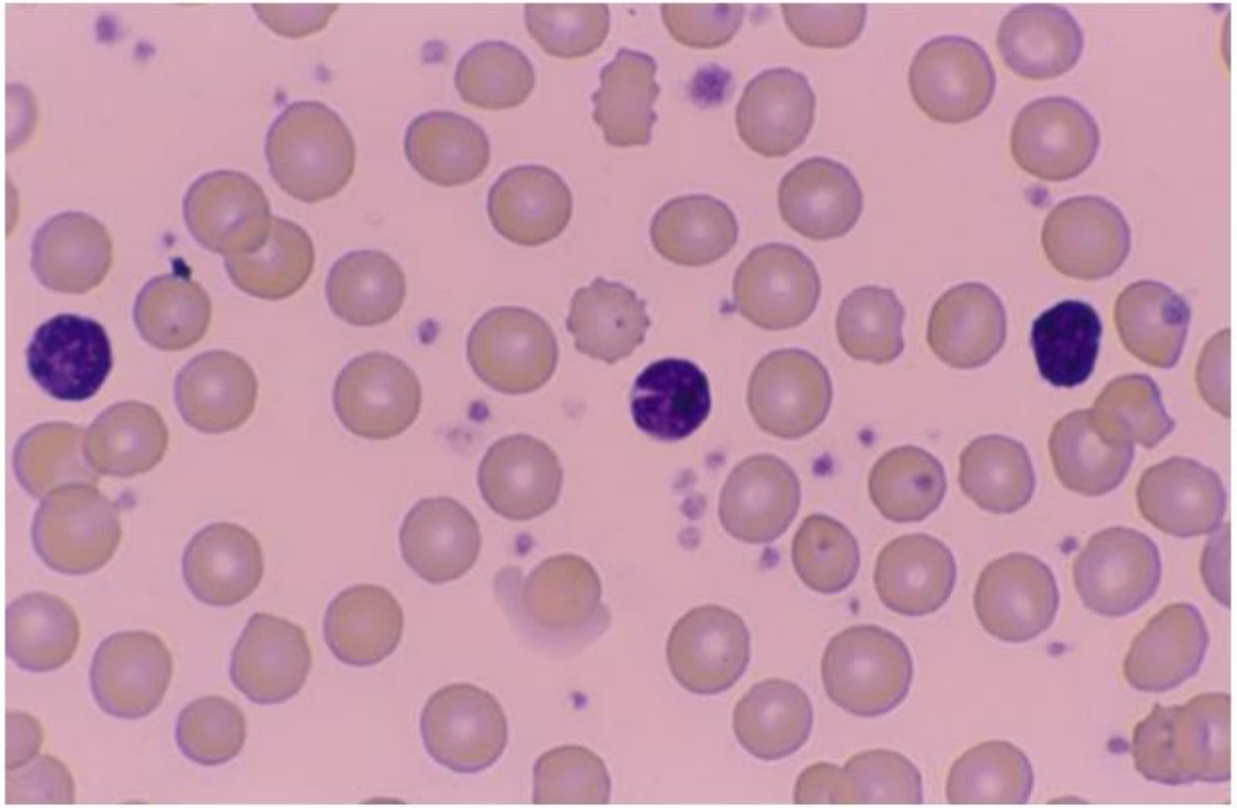


**Figure 10–3 Lymphocytosis (*Bordetella pertussis*).** Lymphocytosis of small mature lymphocytes with prominent nuclear grooves ("buttock cells") in a 3-month-old child with respiratory distress. Immunofluorescent stain on a nasopharyngeal swab demonstrated *Bordetella pertussis*.

## Table 10.1 White Cell Terminology

- **Neutrophilia** Increase in segmented neutrophils
- **Leukocytosis** Increase in white cells
- **Left shift** Increase in bands and metamyelocytes in the peripheral smear; seen in response to infection
- **Leukemoid reaction** Exaggerated response to infection; resulting in high white count and increased numbers of metamyelocytes, bands, and possibly younger cells
- **Leukoerythroblastic picture** Immature white cells, immature red cells, and platelet abnormalities seen in the peripheral smear

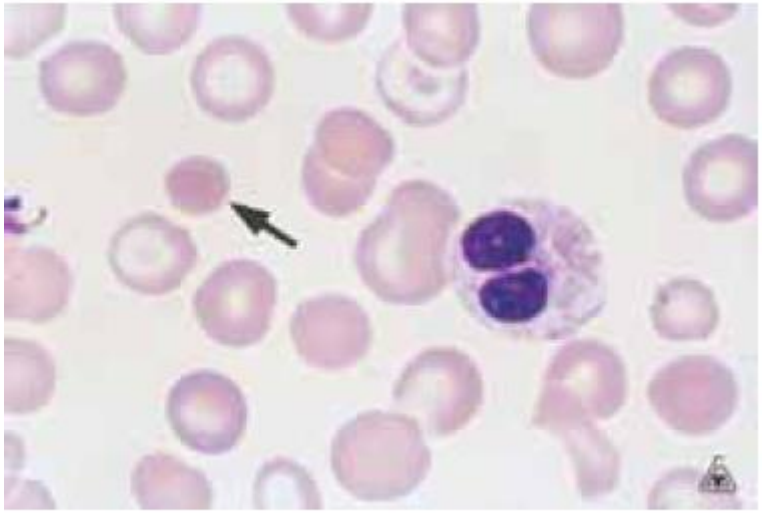


Figure 10.9 Pelger-Huët. Note spherocyte (at *arrow*) and the typical bilobed appearance of Pelger-Huët cells.

## Table 32–4 Morphologic Alterations in Neutrophils

**Toxic granulation** — azurophilic cytoplasmic granules seen in severe infections, other toxic conditions and reactive conditions

**Cytoplasmic vacuoles** — seen in infection, indicating phagocytosis

**Döhle bodies** — pale blue, oval cytoplasmic remnants of ribosomes seen in infections and other toxic conditions

**May–Hegglin anomaly** — rare autosomal dominant condition with pale blue cytoplasmic ribosomal inclusions *resembling* Döhle bodies

**Alder–Reilly anomaly** — prominent azurophilic granulation not related to infection

**Pelger–Huët anomaly** — bilobed or rounded nuclei with pince-nez shape

**Chédiak–Higashi syndrome** — autosomal recessive disorder with giant granules, likely representing giant fused lysosomes, and abnormal leukocyte function

## Table 10.3 Significant Alterations in Neutrophils in Peripheral Smears

- Döhle bodies
- Toxic granulation
- Toxic vacuolization
- Hyposegmentation
- Hypersegmentation
- Bacteria (intracellular or extracellular)
- Platelet satellitism
- Chediak-Higashi granules

## Congenital Disorders of Neutrophil Function

| Disorder | Deficiency | Inheritance | Manifestations |
|---|---|---|---|
| Chronic granulomatous disease (CGD) | NADPH oxidase; cytochrome *b* subunit | Majority X-linked (~75%); remainder autosomal recessive | Recurrent infections with catalase-positive organisms; granulomatous inflammation at site of infections |
| Myeloperoxidase (MPO) deficiency | Myeloperoxidase | Autosomal recessive | May have disseminated *Candida* or other fungal infections, particularly in diabetics; majority of patients have no increase in infections |
| Leukocyte adhesion deficiency type 1 | $\beta_2$ integrin chain (CD18) | Autosomal recessive | Recurrent pyogenic infections (gingivitis, periodontitis) without neutrophil response; persistent neutrophilia |
| Chédiak-Higashi syndrome | Granule fusion | Autosomal recessive | Partial oculocutaneous albinism; large lysosomal granules in PMNs, monocytes, melanocytes and other cells; increased susceptibility to pyogenic infections; may terminate as lymphoma-like accelerated phase |
| Specific granule deficiency | Absence of secondary granules | Autosomal recessive | Recurrent skin and sinus infections, predominantly with staphylococci |
| Alder-Reilly anomaly | Incomplete degradation of mucopolysaccharides | Autosomal recessive | Large purple granules in PMNs, lymphocytes, and monocytes; normal neutrophil function, with no increased susceptibility to infection; associated with mucopolysaccharidoses (Hunter's and Hurler's syndromes) |
| May-Hegglin anomaly | | Autosomal dominant | Large pale blue granules in PMNs resembling Döhle's bodies; thrombocytopenia with giant platelets; defects in platelet function; no increase in infections |
| Pelger-Huët anomaly | | Autosomal dominant | Majority of PMNs have bilobed nuclei ("pince nez" cells), with a few trilobed nuclei; coarse nuclear chromatin; no increase in susceptibility to infection |

*Table 10–4*

## Acquired Neutrophil Dysfunction

| Defects in Chemotaxis | Decreased Phagocytosis due to Impaired Opsonization |
|---|---|
| Autoimmune disorders: SLE, rheumatoid arthritis, polymyositis | Multiple myeloma |
| Diabetes mellitus | Acquired hypogammaglobulinemia |
| Sarcoidosis | Asplenism |
| Leprosy | |
| Hodgkin's disease | |
| Severe malnutrition | |
| Hemodialysis | |
| Severe hypophosphatemia | |
| Graft-versus-host disease | |
| Treatment with antithymocyte globulin (ATG) | |

*Table 10–5*

## Laboratory Evaluation of Possible Neutrophil Disorder

| |
|---|
| Complete blood count and differential |
| Review of blood smear |
| Nitroblue tetrazolium test and stain for myeloperoxidase |
| Expression of CD18, CD11a, CD11b, or CD11c by flow cytometry |

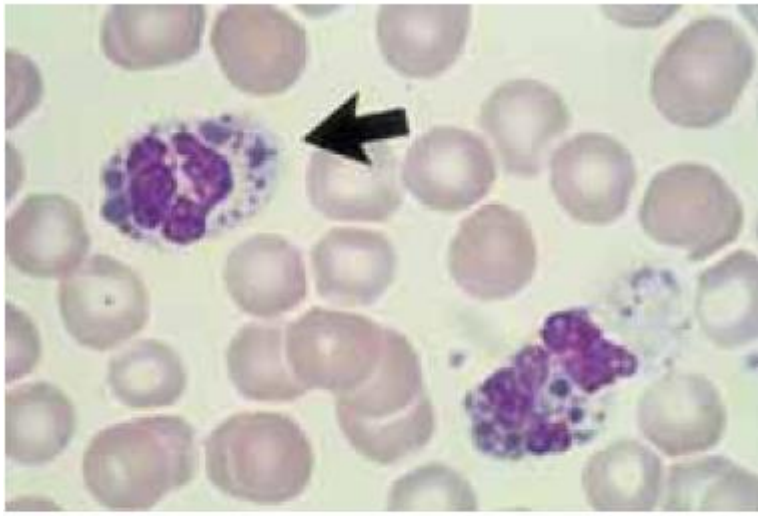


Figure 10.10 Chediak-Higashi anomaly. Note large gray-green granules in the cytoplasm.

**Table 10.4 Lymphocyte Morphologies**

| | Reactive Lymphocyte | Resting Small Lymphocyte |
|---|---|---|
| Size | Large (9 to 30 µm) | Small (8 to 12 µm) |
| N:C ratio | Low to moderate | High to moderate |
| Cytoplasm | Abundant, colorless to dark blue | Scant, colorless to light blue |
| Nucleus | Round to irregular | Round |
| Chromatin | Coarse to moderately fine | Coarse |
| Nucleoli | Absent to distinct | Absent |
| Typing | Polyclonal | Polyclonal |

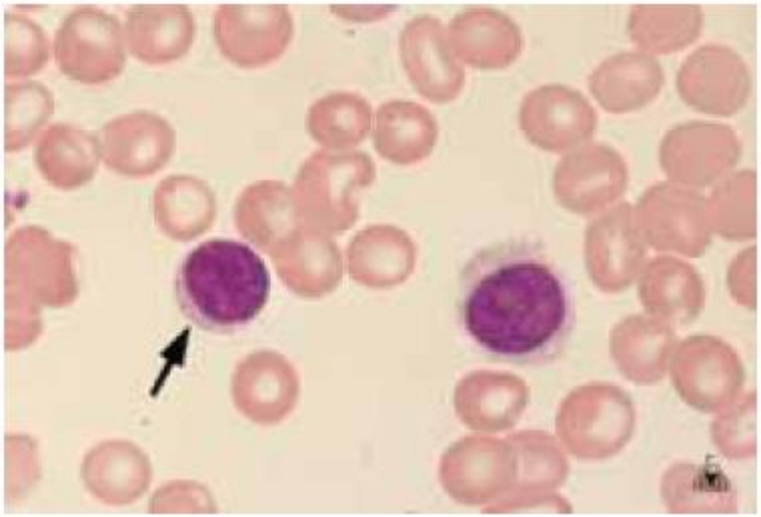


Figure 10.11 Normal lymphocyte.

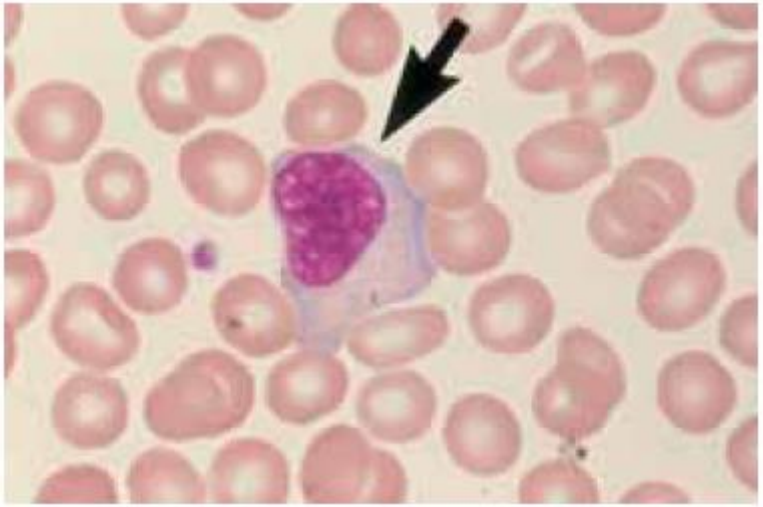


Figure 10.12 Reactive lymphocytes.

*Table 10–6*

## Features That Distinguish Leukemoid Reactions from Leukemia

| Feature | Leukemoid Reaction | Leukemia |
|---|---|---|
| WBC count | Usually ≤75,000/μL | Often ≥75,000/μL |
| Immature cells | Usually absent | Often present |
| Nucleated RBCs | Usually absent | Sometimes present |
| Thrombocytopenia | Usually absent | Often present |
| Lymphadenopathy, splenomegaly | Usually absent | May be present |
| Serum cobalamin (vitamin $B_{12}$) level | Normal | Often increased in chronic myelogenous leukemia (CML) and other myeloproliferative disorders |
| Cytogenetic abnormalities | Absent | Often present |
| Leukocyte alkaline phosphatase (LAP) score | Increased | Decreased in CML; may be increased in other chronic myeloproliferative disorders |

## Table 10.5 Enzyme Deficiencies in Specific Lipid Storage Diseases

| Disease | Missing Enzyme |
|---|---|
| Gaucher's disease | β-Glucocerebrosidase |
| Niemann-Pick disease | Sphingomyelinase |
| Tay-Sachs disease | Hexosaminidase A |

## Table 11.1 Comparison of Characteristics of Acute and Chronic Leukemia

| Characteristic | Acute Leukemia | Chronic Leukemia |
|---|---|---|
| Onset | Abrupt | Subtle |
| Morbidity | Months | Years |
| Age | All | Adults |
| WBC | Variable | Elevated |
| Predominant cells | Blasts and other immature white cells | Mature |
| Anemia, thrombocytopenia | Present | Variable |
| Neutropenia | Present | Variable |
| Organomegaly | Mild | Marked |

## Table 11.5 Immunophenotypic Classification

| Lineage | Marker |
|---|---|
| Hematopoietic precursor | CD117 (HLA-DR), CD34 |
| Myeloid | CD11b, CD13, CD33, CD15 |
| T-lineage | CD1, CD2, CD3, CD4, CD5, CD7, CD8, TdT |
| B-lineage | CD10, CD19, CD20, CD21A, CD22, CD23, CD24, CD79a, TdT |
| Erythroid | Glycophorin A |
| Monocytic | CD14, CD4, CD11b, CD11c, CD36, CD64 |
| Megakaryocytic | CD41, CD42, CD61 |

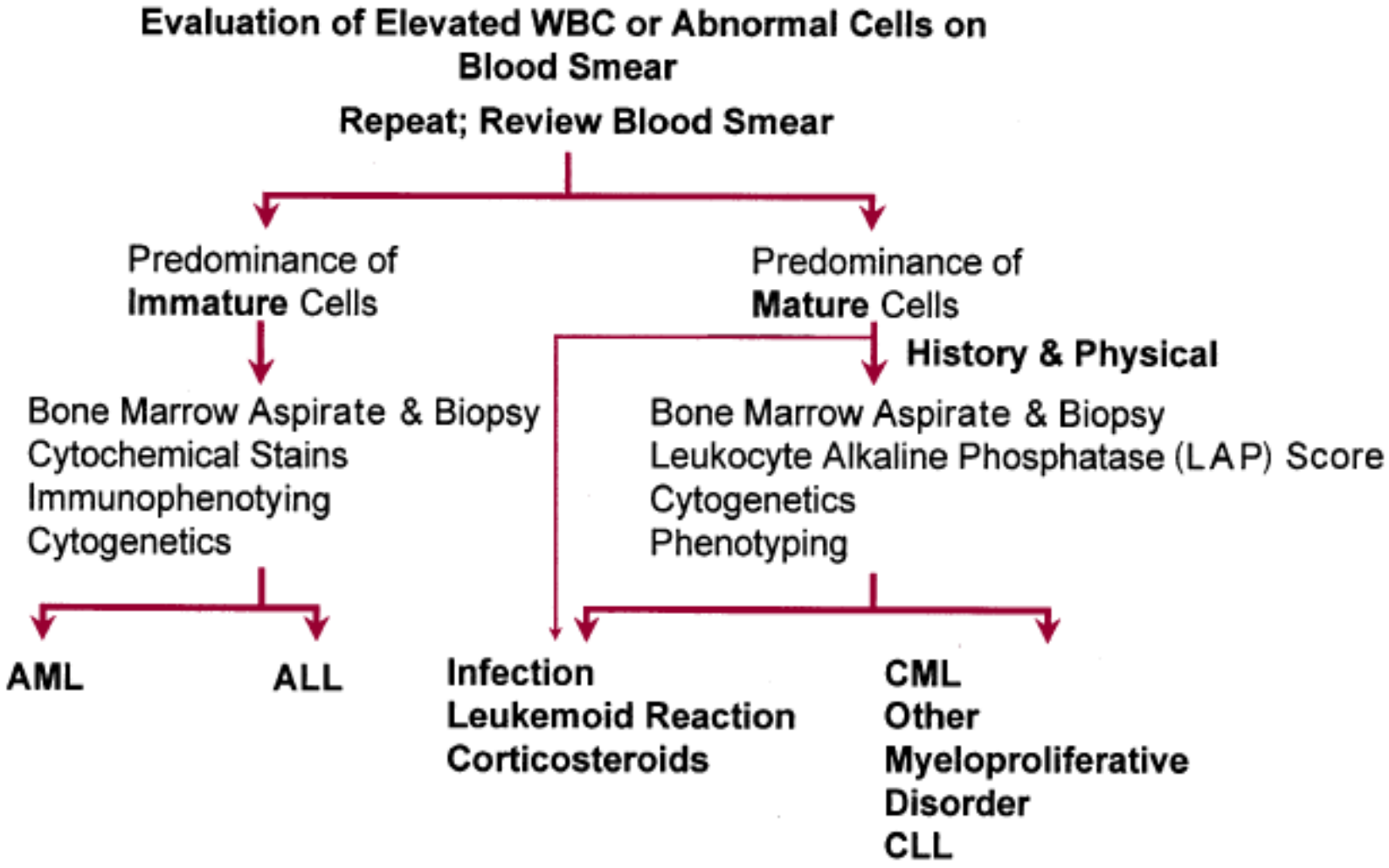



**Figure 10–4** Evaluation of elevated WBC or abnormal cells on blood smear.

(a) Pathogenesis of haematological malignancy.

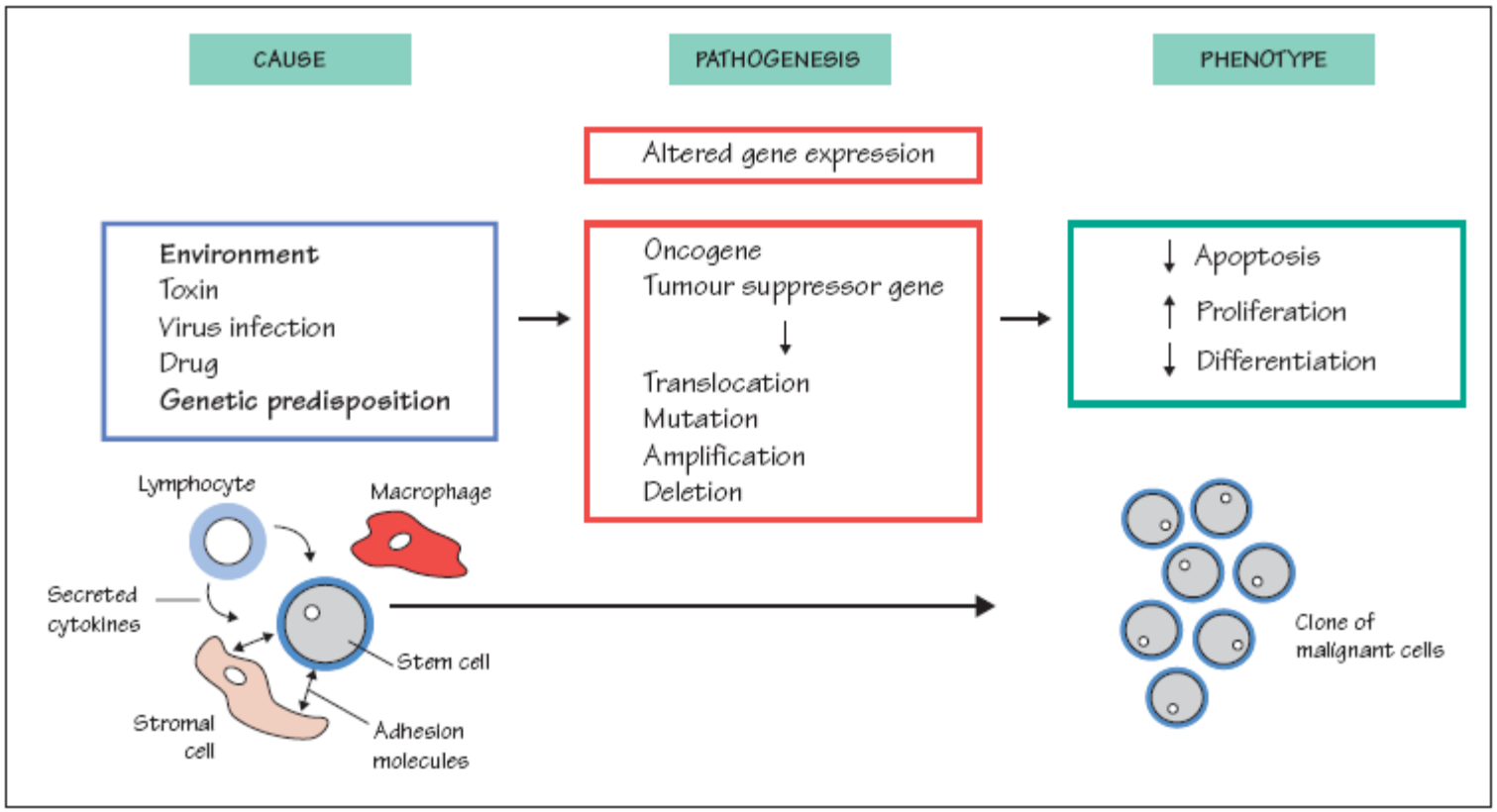



**Table 20.1** Classification of haematological malignancies.

| | Acute | Chronic |
|---|---|---|
| Lymphoid | Acute lymphoblastic leukaemia (ALL) and subtypes | Chronic lymphocytic leukaemia<br>Non-Hodgkin lymphoma (NHL)<br>Hodgkin lymphoma (HL)<br>Multiple myeloma and variants |
| Myeloid | Acute myeloid leukaemia (AML) and subtypes | Chronic myeloid leukaemia (CML)<br>Myelodysplasia (MDS)<br>Myeloproliferative disorders |

*Table 12–2*

## Classification Systems for Hematopoietic Diseases

| | Older Classification Systems | Newer Classification Systems |
|---|---|---|
| **Non-Hodgkin's Lymphomas** | • Rappaport<br>• Working Formulation<br>• Updated Kiel | • Revised European American Lymphoid Classification (REAL)<br>• WHO* |
| **Hodgkin's Lymphoma** | • Rye | • WHO |
| **Acute Leukemias (AML & ALL)** | • French-American-British (FAB) | • WHO |
| **Chronic Leukemias** | • French-American-British (FAB)<br>• Polycythemia Vera Study Group | • WHO |

*World Health Organization.

## Table 11.2 Conditions and Disorders With Increased Risk for Development of Acute Leukemia

| Congenital Defects | Acquired Diseases | Environmental Factors |
|---|---|---|
| Down syndrome | Aplastic anemia | Ionizing radiation |
| Klinefelter syndrome | Myeloma | Alkalating agents |
| Turner syndrome | Sideroblastic anemia | Cytotoxic drugs |
| Monosomy 7 syndrome | Acquired genetic changes | Pesticide exposure |
| Fanconi's anemia | Translocations | Solvents |
| Wiskott-Aldrich syndrome | Inversions | |
| Neurofibromatosis | Deletions | |
| Familial aplastic anemia | Point mutations | |
| Fraternal twins and nonidentical siblings | Paroxysmal nocturnal hemoglobinuria | |
| Combined immunodeficiency syndrome | Transition from other hematopoietic diseases (myeloproliferative disorders) | |
| Blackfan-Diamond syndrome | | |

## Table 11.3 Clinical Findings in Acute Leukemia

| Pathogenesis | Signs and Symptoms |
|---|---|
| *Bone Marrow Infiltration* | |
| Neutropenia | Fever, infection |
| Anemia | Pallor, dyspnea, lethargy |
| Thrombocytopenia | Bleeding, petechiae, ecchymosis, intracranial hematoma and gastrointestinal or conjunctival hemorrhage (rare) |
| *Medullary Infiltration* | |
| Marrow | Bone pain and tenderness, limp, arthralgia |
| *Extramedullary Infiltration* | |
| Liver, spleen, lymph nodes, thymus | Organomegaly |
| Central nervous system | Neurological complications including dizziness, headache, vomiting, alteration of mental function |
| Gums, mouth | Gingival bleeding and hypertrophy |
| Skin | Lesions or granulocytic sarcoma |

**Table 23.3** Immunophenotypes of acute leukaemia.

| Disease | Immunophenotype |
|---|---|
| AML | CD33, CD13, CD117<br>Monocytic cells: CD14, CD61<br>Megakaryoblasts: CD41, CD61<br>Erythroid: glycophorin, transferrin receptor (CD71) |
| ALL | |
| Early B-precursors (Pro-B) | CD19, TdT |
| Common ALL | CD10, CD19, cyt CD22, TdT |
| Pre B-ALL | cyIg, CD19, cyt CD22, TdT |
| B-ALL | sMIg, CD19, CD20 |
| T-ALL | CD7, cytCD3, TdT |

CD34 is a marker of haemopoietic stem cells and may be positive in both AML and ALL.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; B-ALL, B cell ALL; CyIg, cytoplasmic immunoglobin; sMIg, surface membrane immunoglobuli; T-ALL, T cell ALL; TdT, terminal deoxynucleotidyl transferase.

## Table 11.4 Cytochemical Reactions in Acute Leukemia

| Cytochemical Reaction | Cellular Element Stained | Blasts Identified |
|---|---|---|
| Myeloperoxidase (MPO) | Neutrophil primary granules | Myeloblasts strong positive; monoblasts faint positive |
| Sudan Black B (SBB) | Phospholipids | Myeloblasts strong positive; monoblasts faint positive |
| Specific esterase | Cellular enzyme | Myeloblasts strong positive |
| Nonspecific esterase (NSE) | Cellular enzyme | Monoblasts strong positive |
| Terminal deoxynucleotidyl transferase (TdT) | Intranuclear enzyme | Lymphoblasts positive |
| Periodic acid-Schiff | Glycogen | Variable, coarse or block-like positivity often seen in lymphoblasts and pronormoblasts, myeloblasts usually negative although faint diffuse reaction may occasionally be seen |

## Table 11.8 Chromosomal Alterations*

| Chromosome Abnormality | Clinical Correlation |
|---|---|
| AML | t(8;21)(q22;q22)<br>11q23<br>Trisomy 7, 8, 13 |
| AML with abnormal bone marrow eosinophils | inv(16)(p13q22)<br>t(16;16)(p13;q22) |
| APL | t(15;17)(q22;q12) |
| AMML | t(8;16)(p11;p13) |
| AMonoL | t(9;11)(p22;q23) |
| B-ALL | Hyperdiploid >50<br>t(1:19)(q23;p13.3)<br>t(12;21)(p13;q22) |
| T-ALL | t(1;14)(p32;q11.2)<br>t(1;7)(q32;q35) |

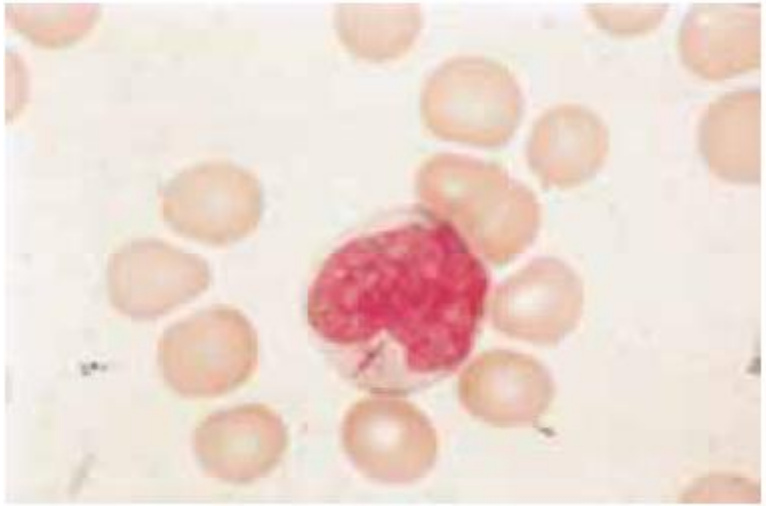


**Figure 11.2** Acute myeloid leukemia with t(8;21)(q22;q22). Note Auer rod in myeloblast.

## Table 11.6 FAB Classification of Acute Leukemia

| Designation | Descriptive Name |
|---|---|
| M0 | Acute myeloblastic leukemia, minimally differentiated |
| M1 | Acute myeloblastic leukemia without maturation |
| M2 | Acute myeloblastic leukemia with maturation |
| M3 | Acute promyelocytic leukemia, hypergranular |
| M3v | Acute promyelocytic leukemia, microgranular |
| M4 | Acute myelomonocytic leukemia |
| M4Eo | Acute myelomonocytic leukemia with eosinophilia |
| M5a | Acute monoblastic leukemia, poorly differentiated |
| M5b | Acute monoblastic leukemia, with differentiation |
| M6 | Erythroleukemia |
| M7 | Acute megakaryoblastic leukemia |
| L1* | Acute lymphoblastic leukemia |
| L2* | Acute lymphoblastic leukemia |
| L3* | Acute lymphoblastic leukemia, leukemic phase of Burkitt's lymphoma |

*Based on blast morphology.

## Table 11.7 World Health Organization Classification of Acute Myeloid Leukemias

Acute myeloid leukemia with recurrent genetic abnormalities
- Acute myeloid leukemia with t(8;21)(q22;q22)
- Acute myeloid leukemia with abnormal bone marrow eosinophils
  - inv(16)(p13q22) or t(16;16)(p13;q22)
- Acute promyelocytic leukemia (AML with t(15;17)(q22;q12)
- Acute myeloid leukemia with 11q23

Acute myeloid leukemia with multilineage dysplasia

Acute myeloid leukemia and myelodysplastic syndromes, therapy-related

Acute myeloid leukemia not otherwise categorized
- Acute myeloid leukemia minimally differentiated
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic and monocytic leukemia
- Acute erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma

Acute leukemia of ambiguous lineage
- Undifferentiated acute leukemia
- Bilineal acute leukemia
- Biphenotypic acute leukemia

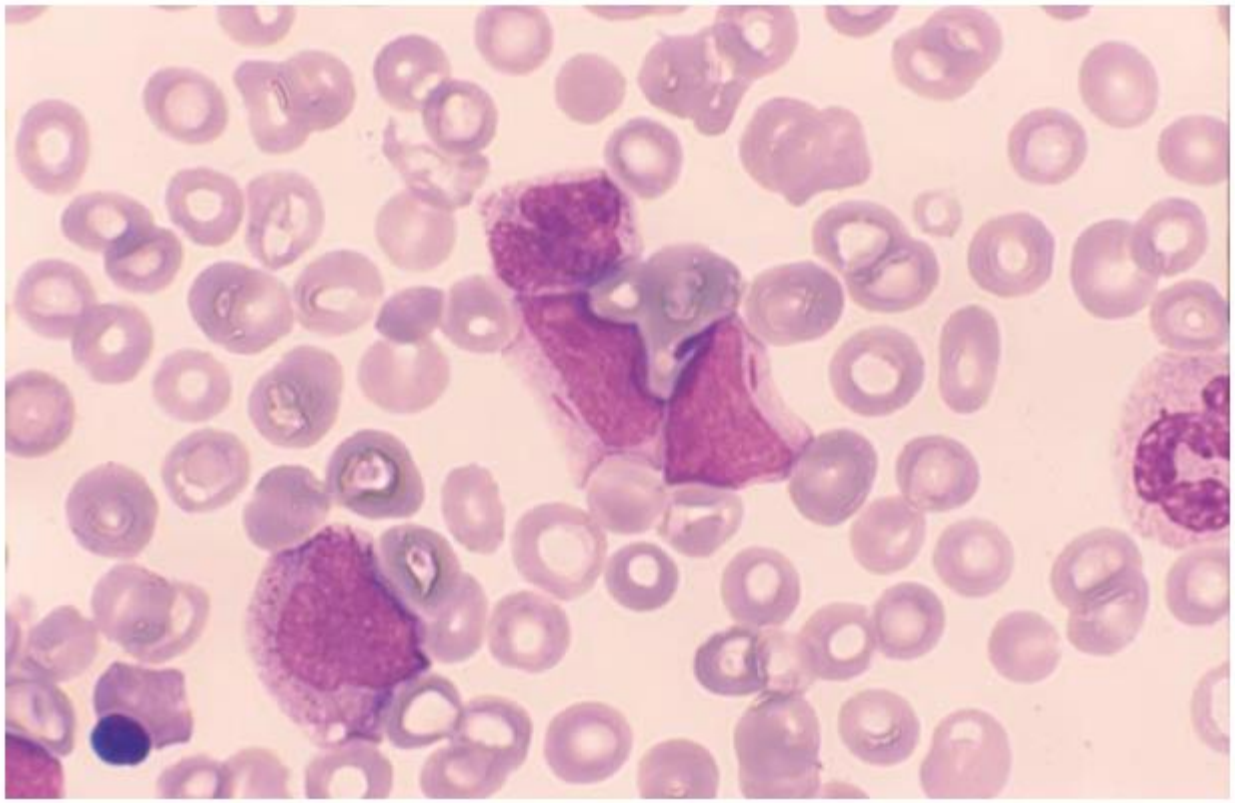


**Figure 13–4 Acute myelogenous leukemia (AML) blood smear.** The two cells in the center contain Auer rods.

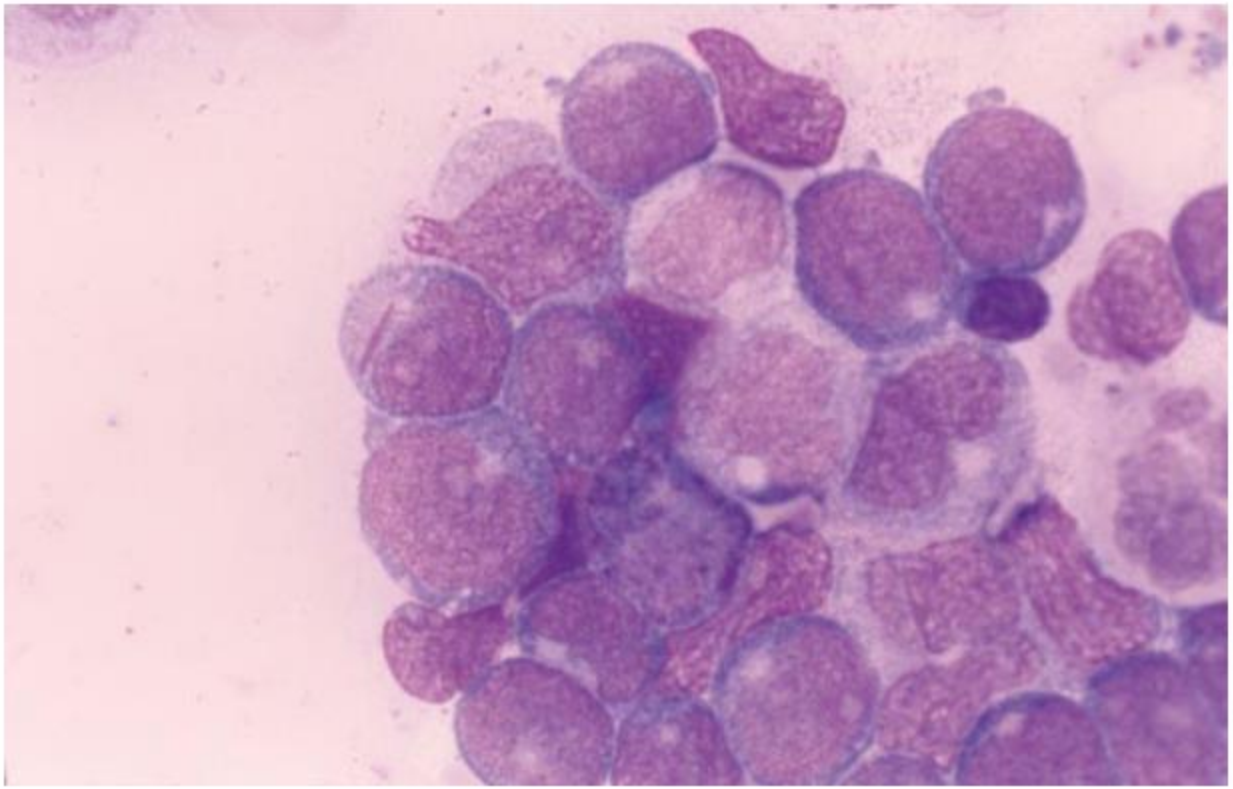


**Figure 13–5 Acute myelogenous leukemia (AML) bone marrow aspirate.** Note the prominent Auer rod in the cell on the edge of the cluster.

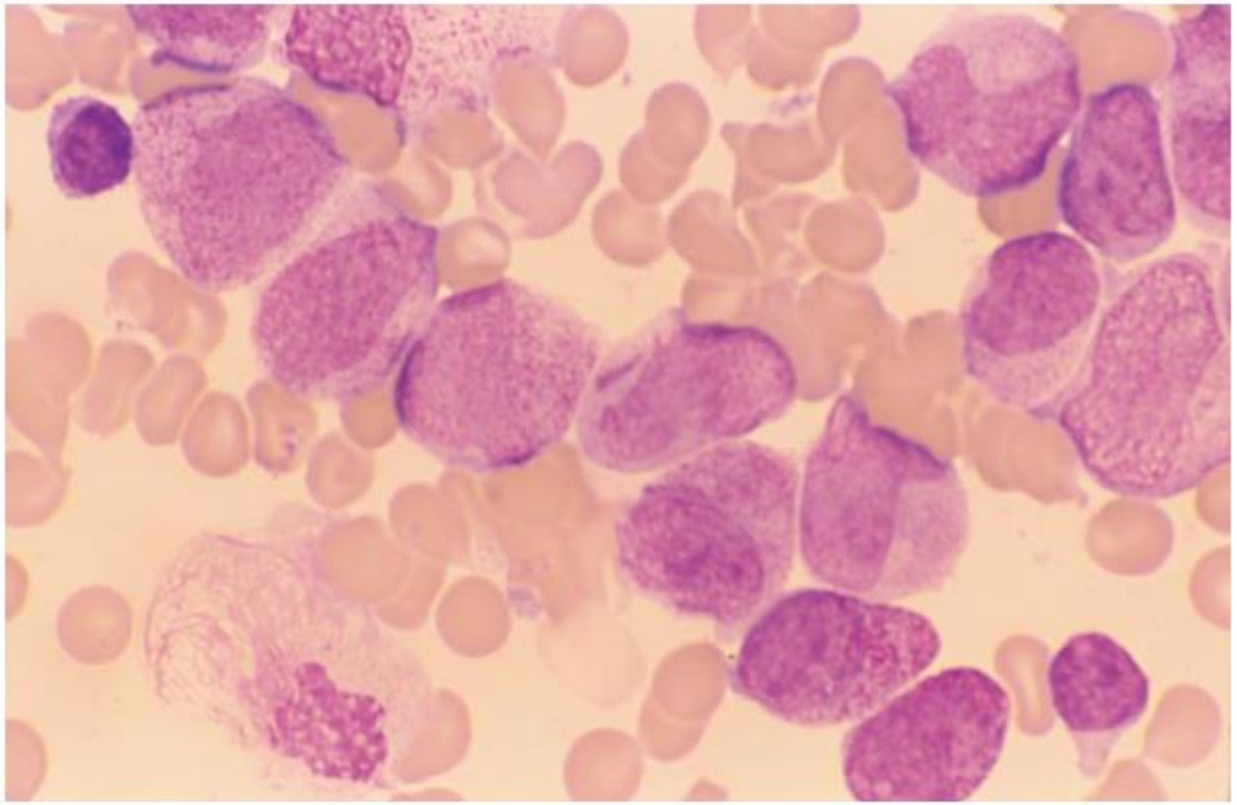


**Figure 13–7** **Acute promyelocytic leukemia (FAB AML-M3) bone marrow aspirate.** Note the prominent Auer rod in the center cell.

Table 32–15 Key Features of the Major Acute Myeloid Leukemias (AML)

| Category | Cell morphology | Cell surface markers | Cytogenetics | Prognosis |
|---|---|---|---|---|
| AML with t(8;21) | Large blasts, with abundant basophilic cytoplasm, Auer rods, dysplasia, abnormal granules, maturing granulocytes | CD 13, 33,117, CD19, CD34 | t(8;21)(q22;q22) *AML1/ETO* | More favorable than AML without recurrent genetic abnormality |
| AML with inv(16) | Blasts with both monocytic and neutrophilic differentiation, increased eosinophils/immature eosinophils | CD 13, 33, 14, 4, 64 | inv(16)(p13;q22) or t(16;16)(p13;q22) | Superior to other AML |
| Acute promyelocytic leukemia | Promyelocytes with azurophilic granules, Auer rods | CD 13, 33<br>CD2±, DR– | t(15;17)(q22;q12)<br>*PML/RARα*<br>Variants all involve 17q12 | Good if responsive to ATRA |
| AML with 11q23 | Variable. Monocytic differentiation seen in t(9;11) | CD 13, 33, 34, ± 56, 57.<br>CD 14, 4, 36 with monocytic differentiation | t(9;11)(p22;q23), others | Less favorable than other AML |
| AML, therapy related | Multilineage dysplasia, RS, increased basophils | CD 13, 33, 34, ± 56, 57 | 11q23 abnormality seen with topoisomerase II inhibitor-associated AML | Median survival < 3 years |
| **AML, not otherwise categorized** | | | | |
| AML, minimally differentiated | M0 in FAB. Myeloblasts, < 3% positive for SBB, MPO or ANA | CD 13, 33, 117 in ≥ 20% of blasts | Nonspecific/not available | Poor |
| AML without maturation | M1 in FAB. Myeloblasts ≥ 90% of nonerythroids in BM, ≥ 3% positive for SBB or MPO | CD 13, 33, 117 | Nonspecific/not available | Poor |
| AML with maturation | M2 in FAB. Same as for AML with t(8;21) | CD 13, 33, 117 | Nonspecific/not available | Variable. Less favorable than AML with t(8;21) |
| Acute myelomonocytic leukemia | M4 in FAB. Monocytic cells 20–79%, granulocytic 30–80% of nonerythroids | CD 13, 33, 14, 4, 11b, 11c, 64, 36, 68 | Nonspecific/not available | Variable. Less favorable than AML with inv(16) |
| Acute monoblastic/ monocytic | M5 in FAB. ≥ 80% of nonerythroids are monoblasts (M5a) or show monocytic diff (M5b) | CD 13, 33, 117, 14, 4, 11b, 11c, 64, 68, 36 | t(8;16)(p1l; p13) seen in some acute monocytic leukemia cases<br>Nonspecific/not available | Poor |
| Erythroleukemia | M6 in FAB. ≥ 50% erythroblasts and ≥ 20% myeloblasts in nonerythroids. Pure erythroleukemia without myeloid blasts is rare | Glycophorin A, Hb A in erythroid blasts; CD 13, 33, 117 in myeloblasts | Nonspecific | Poor |
| Acute megakaryoblastic leukemia | Polymorphic megakaryoblasts, may simulate lymphoblasts. PB may show megakaryocytic fragments | CD 41, 61, 36, often CD 13, 33 | Nonspecific in adults. Infants may show t(1;22)(p13;q13) | Poor, especially with t(1;22) |

## Table 11.9 FAB Morphological Classification of Acute Lymphoblastic Leukemia

| Feature | L1 | L2 | L3 |
|---|---|---|---|
| Cell size | Small, regular | Large, mixed sizes | Large |
| Nuclear chromatin | Fine or condensed | Fine or condensed | Fine |
| Nuclear shape | Regular, cleft or indentation possible | Irregular, cleft or indentation more common | Regular, round or oval |
| Nucleoli | Indistinct | 1 to 2, prominent | 1 to 2, prominent |
| Cytoplasm | Scant | Variable, often moderately abundant | Deeply basophilic, vacuolated |

## Table 11.10 Prognostic Factors in Acute Lymphoblastic Leukemia

| Risk Factors | Favorable | Unfavorable |
|---|---|---|
| WBC Count | $<10 \times 10^9$/L | $>50 \times 10^9$/L |
| Hemoglobin | <10 g/dL | >7 g/dL |
| Age | 2 to 9 years | <2 and >10 years |
| Race | White | Black |
| Sex | Female | Male |
| Response to treatment | <14 days | >28 days |
| CNS leukemia | Absent | Present |
| Immunophenotype | Precursor B-cell | Precursor T-cell or mixed lineage |
| Cytogenetic | Hyperploidy >50<br>t(12;21)(p13;q22) | Hypoploidy<br>Translocations, especially<br>t(9;22)(q34;q11.2)<br>t(1;19)(q23;p13.3)<br>t(4;11)(q21;q23) |

*Table 13–2*

## WHO Classification of ALL

**Precursor B-cell ALL**:

Cytogenetic subgroups (with oncogenes involved):

t(9;22)(q34;q11); *BCR/ABL* (the *Philadelphia chromosome*)

t(v;11q23); *MLL* rearranged (*MLL* = *myeloid-lymphoid leukemia* gene)

t(1;19)(q23;p13); *E2A/PBX1*

t(12;21)(p12;q22); *TEL/AML1*

**Precursor T-cell ALL**

**Burkitt-cell leukemia**

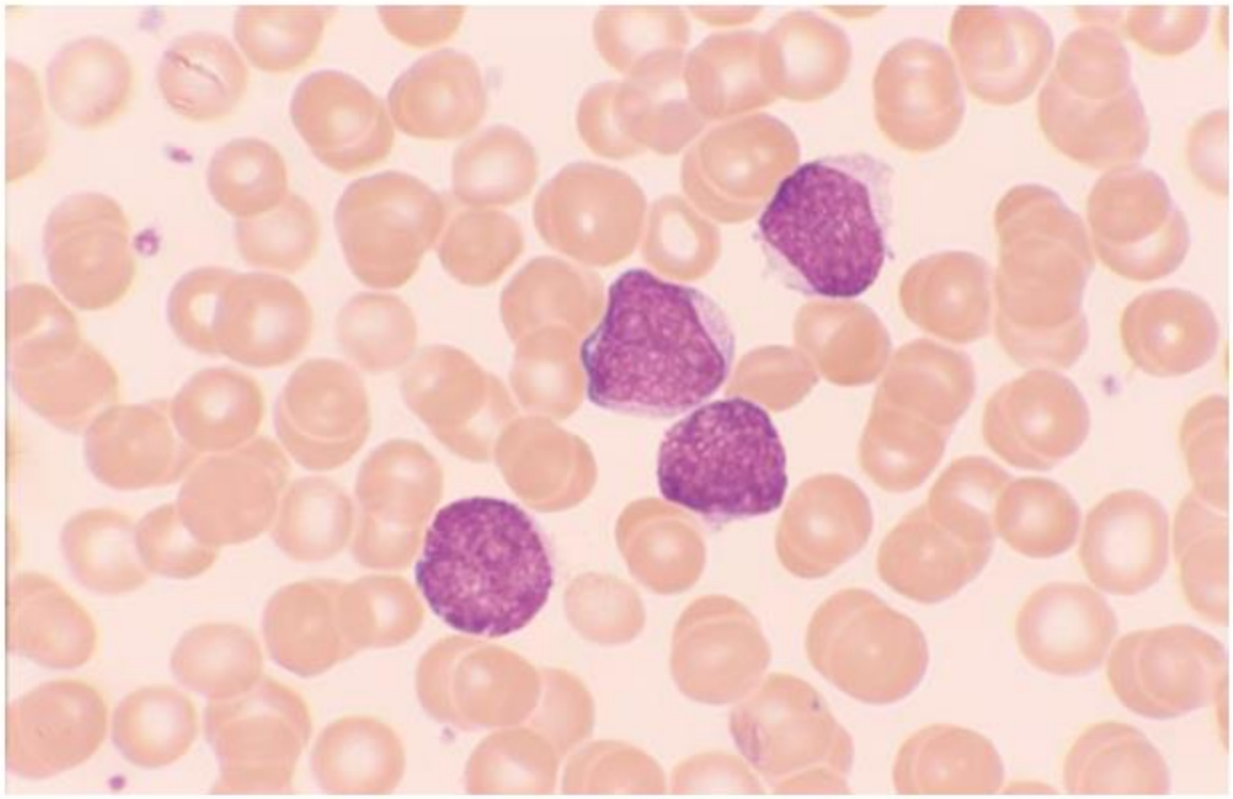


**Figure 13–1** Acute lymphoblastic leukemia (ALL) blood smear.

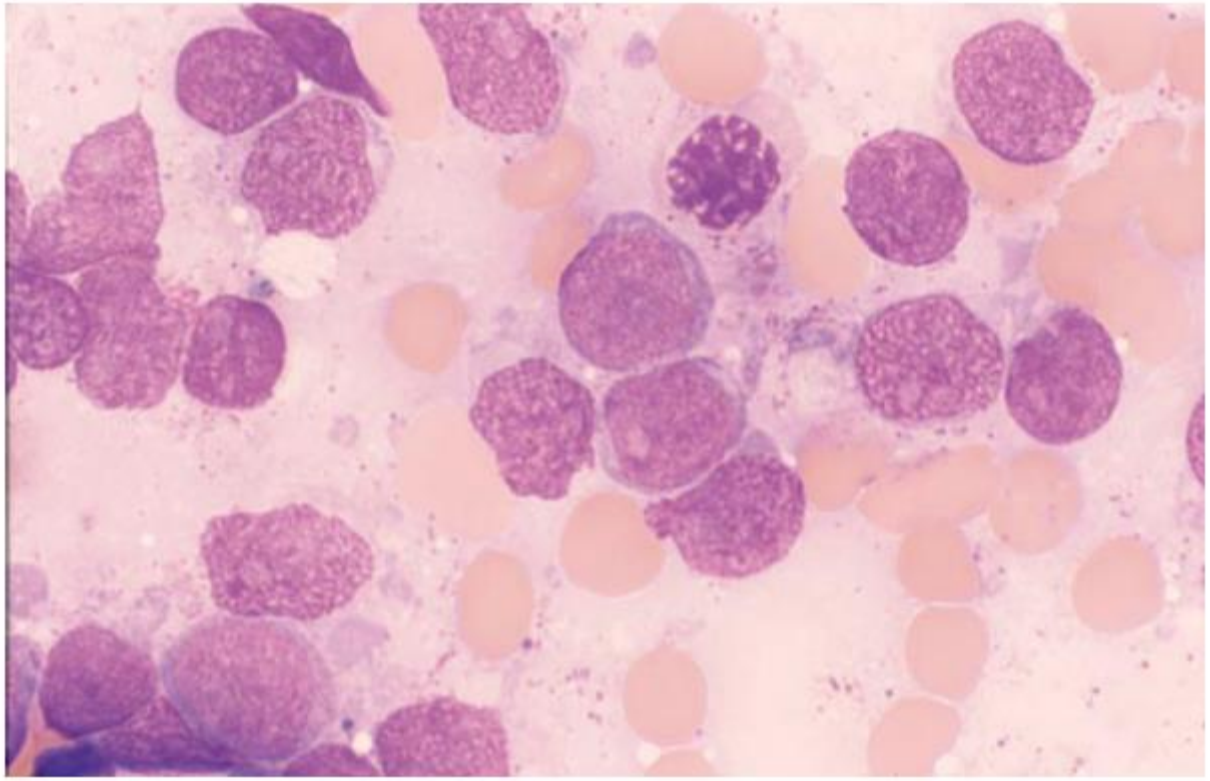


**Figure 13–2** Acute lymphoblastic leukemia (ALL) bone marrow aspirate.

## Important Chromosomal Aberrations in Acute Lymphoblastic Leukemia

| *Translocation* | *Genes involved* | | *Function* | *Frequency* |
|---|---|---|---|---|
| t(9:22) | *BCR* | ↓ | Unknown | Adults 20–30% |
| (q34;q11) | *ABL* | | Tyrosine kinase | Children 5% |
| t(1;19) | *E2A* | | bHLH transcription factor | Adults 2% |
| (q23;pl3) | *PBX1* | | Homeotic | Children 5% |
| t(11;v) | *MLL* | ↓ | Trithorax-like | 3–7% (75% in infants |
| (q23;v) | Variable | | Variable | |
| t(12;21) | *TEL* | ↑ | Ets-like transcription factor | Adults 3% |
| (p13;q22) | *AML1* | | Runt-like transcription factor | Children 25% |
| t(17;19) | *E2A* | | bHLH transcription factor | <1% |
| (q22;p13) | *HLF* | | bZIP transcription factor | |
| t(8;14) | *MYC* | | bHLH transcription factor | 2–5% |
| (q24;q32) | *IgH* | | Immunoglobulin enhancer | |
| t(8;14) | *MYC* | ↑ | bHLH transcription factor | <1% |
| (q24;ql1) | *TCRα* | | T-cell receptor enhancer | |
| t(1;14) | *TAL1/SCL* | ↑ | bHLH transcription factor | <1% |
| (p32;q11) | *TCRδ* | | T-cell receptor enhancer | |
| t(11;14) | *TTG2* | ↑ | LIM protein | 1% |
| (p15;q11) | *TCRδ* | | T-cell receptor enhancer | |
| t(7;9) | *TAN1* | | Notch-like | <1% |
| (q34;q34) | *TCRβ* | | T-cell receptor enhancer | |

↑, Prognostically favorable; ↓, prognostically unfavorable.
bHLH, basic helix-loop-helix; bZIP, basic leucine zipper.
Modified from Sallan et al. Educational brochure, American Society of Hematology, 1997.

## Immunological Classification of Acute Lymphoblastic Leukemias (ALLs)

| *Type of ALL* | *HLA-DR* | *TdT* | *CD10* | *CD19*[a] | *CyIg* | *SIg* | *CD7* | *CyCD3* | *Frequency* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | *Adults* | *Children* |
| Pro-B-ALL | + | + | 0 | + | 0 | 0 | 0 | 0 | 4–10% | 7% |
| Common ALL | + | + | + | + | 0 | 0 | 0 | 0 | 50–60% | 70% |
| Pre-B-ALL | + | + | + | + | + | 0 | 0 | 0 | ≈10% | ≈15% |
| B-ALL | + | 0 | +/– | + | +/– | ++ | 0 | 0 | 3–4% | 2–3% |
| Early T-ALL | 0 | + | 0/+ | 0 | 0 | 0 | + | + | 7–10% | ≈1% |
| T-ALL[b] | 0 | + | 0/+ | 0 | 0 | 0 | + (+CD1a, CD2, CD3) | + | 15–20% | ≈10% |

CD, cluster of differentiation (*see* Appendix 2); CyIg, cytoplasmic immunoglobulin; SIg, surface immunoglobulin; CyCD3, cytoplasmic CD3.

[a]As accessory markers for B-lineage, CD79a and/or CD22 are useful.

[b]The subtype of thymic (cortical) ALL is characterized by the CD1a and has a better prognosis in adult patients

## Table 12.1 WHO Classification of Chronic Myeloproliferative Diseases

Chronic myelogenous leukemia [Ph chromosome, t(9;22) (q34;q11). *BCR-ABL* positive]

Chronic neutrophilic leukemia

Chronic eosinophilic leukemia (hypereosinophilic syndrome)

Polycythemia vera

Chronic idiopathic myelofibrosis

Essential thrombocythemia

Chronic myeloproliferative disease unclassifiable

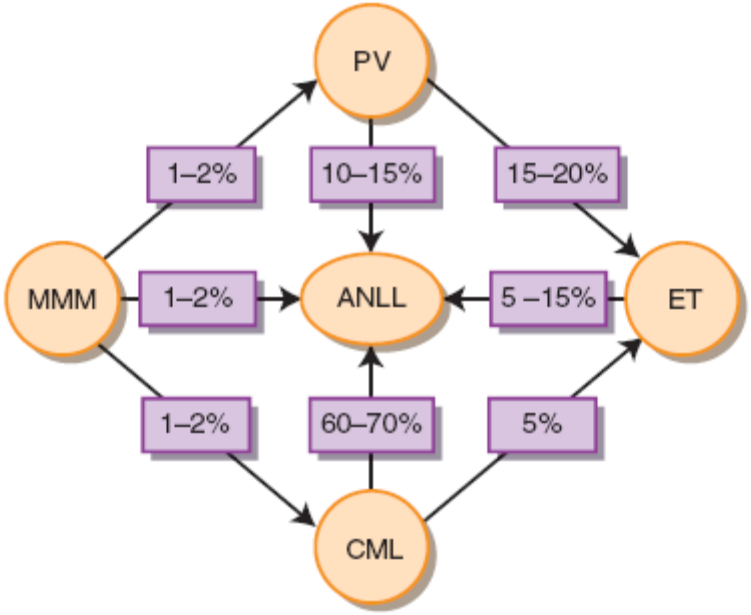
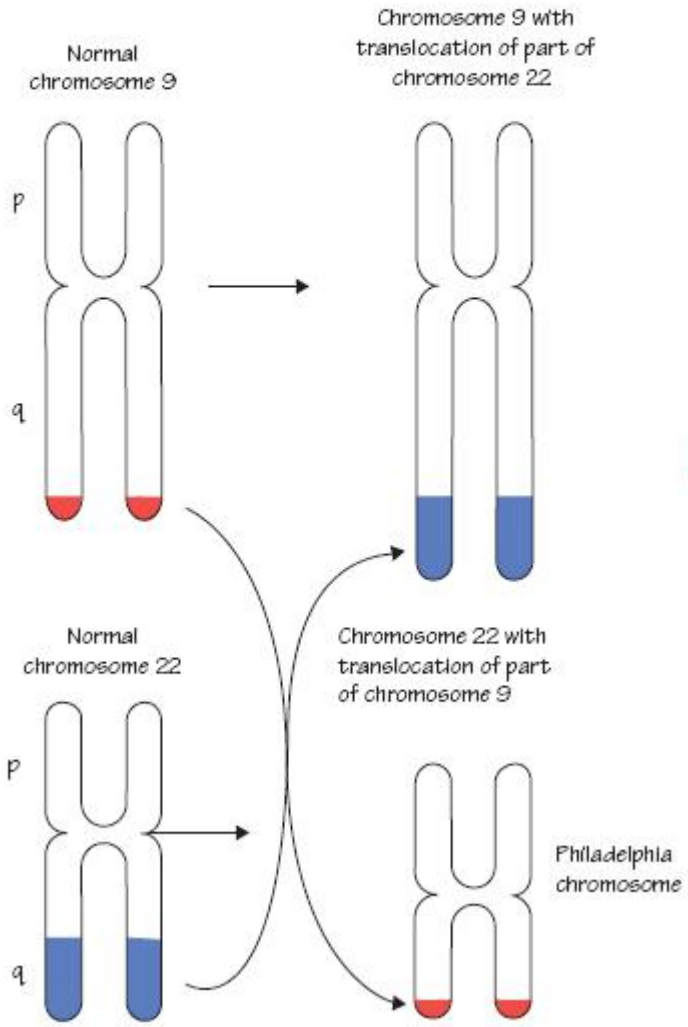



**Figure 12.1** Interrelationships of the CMPDs.

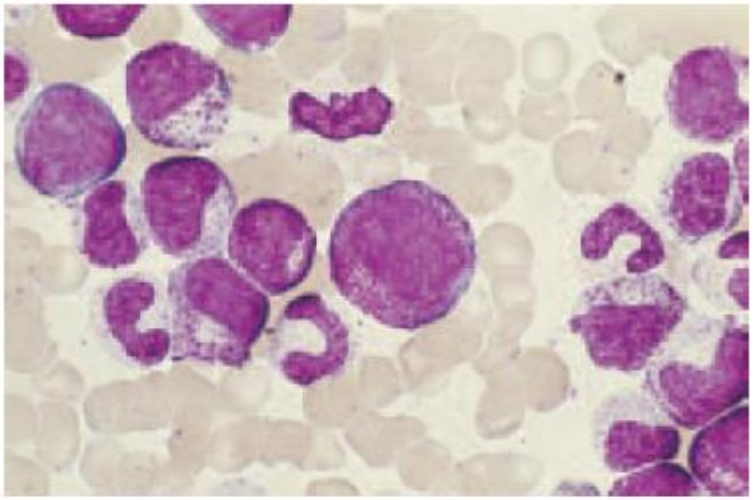
## Table 12.2 Characteristics of Chronic Myeloproliferative Disorders

| CMPD | Cell Line | WBC | Bone Marrow Fibrosis | Philadelphia Chromosome ($Ph^1$) | Organ Involvement |
|---|---|---|---|---|---|
| Chronic myelogenous leukemia (CML) | Myeloid | Increased | Variable | Present | Splenomegaly Hepatomegaly |
| Polycythemia vera (PV) | Erythroid, myeloid megakaryocyte | Increased | None | Absent | Splenomegaly Hepatomegaly |
| Myelofibrosis with myeloid metaplasia (MMM) | Teardrop, erythrocytes Fibroblasts | Variable | Increased | Absent | Splenomegaly Hepatomegaly |
| Essential thrombocythemia (ET) | Megakaryocyte | Normal | None | Absent | Splenomegaly |

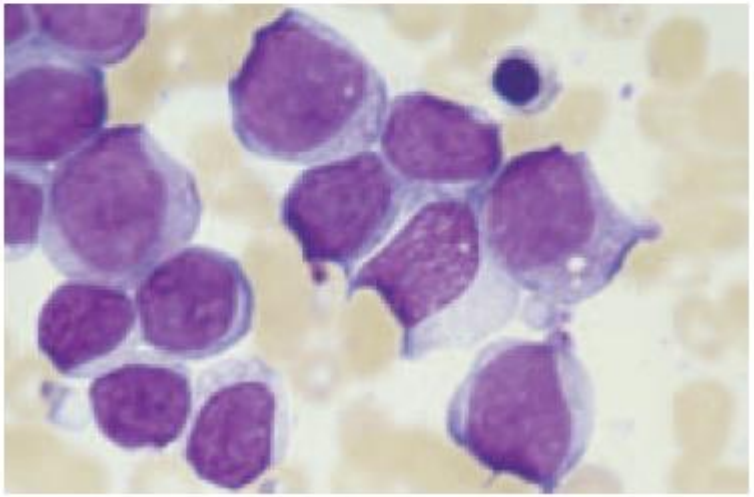
(a) The Philadelphia chromosome is an abnormal chromosome 22 caused by translocation of part of long arm (q) of chromosome 22 to chromosome 9, and reciprocal translocation of part of chromosome 9, including the ABL oncogene, to a specific breakpoint cluster region (BCR) of chromosome 22. A fusion gene results on the derived chromosome 22 which leads to the synthesis of an abnormal protein with tyrosine protein kinase activity that is much greater than that of the normal ABL protein.




(b) Chronic myeloid leukaemia (chronic phase): peripheral blood film, showing immature granulocytes (myelocytes, metamyelocytes) in the peripheral blood.



(c) Chronic myeloid leukaemia: blast transformation. There is replacement by homogenous blast cells.



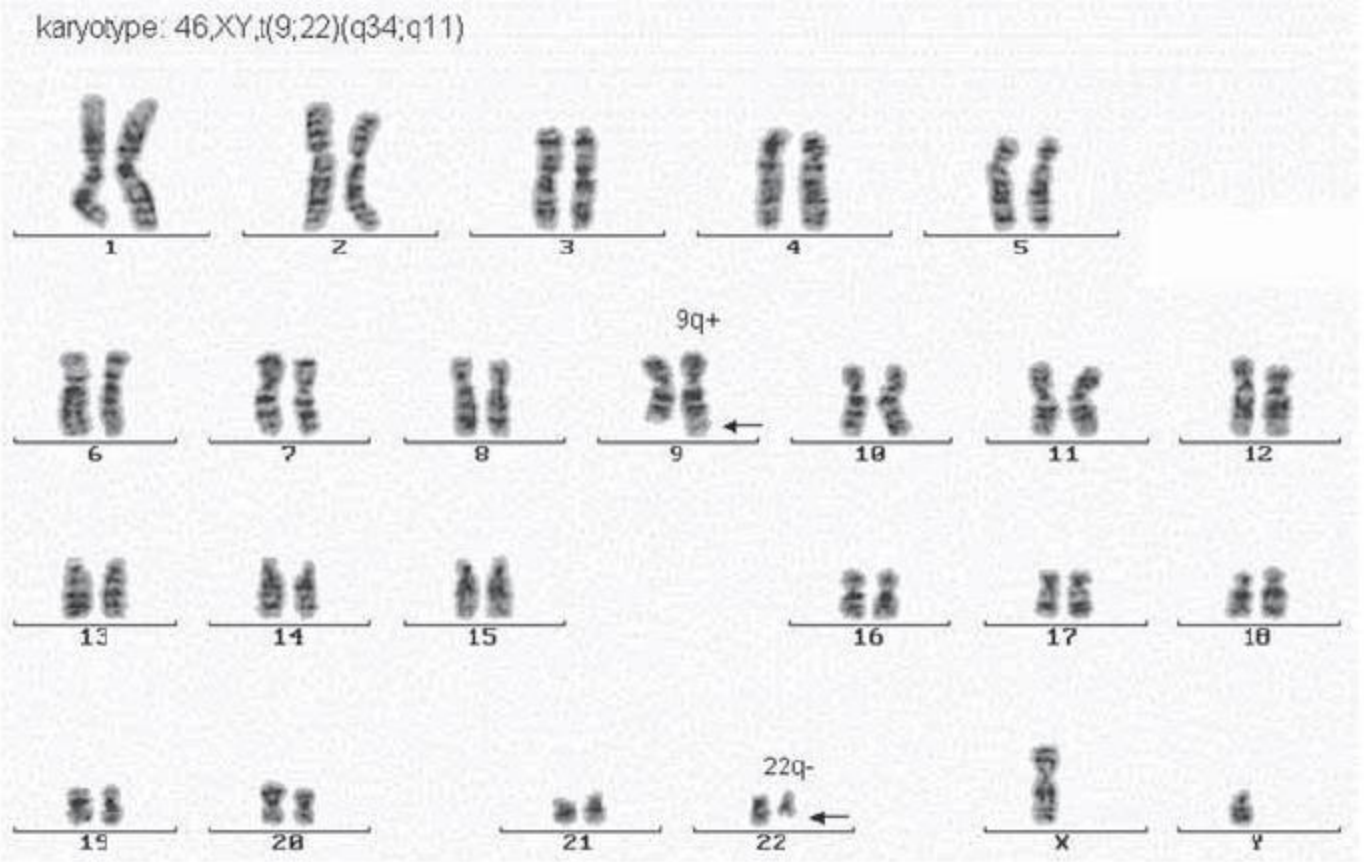



Fig. 8.1. Chronic myelogenous leukemia. Karyotype showing t(9;22).

## Table 12.3 Key Facts of CML

- Clonal stem cell disorder
- Marked leukocytosis with all stages of granulocyte maturation
- Hepatosplenomegaly
- Thrombocytosis is common in chronic phase
- Three phases: chronic, accelerated, blast
- Philadelphia chromosome
- *BCR-ABL* fusion gene
- LAP score <10

## Table 12.6 Key Facts of Polycythemia Vera

- Increase in all three cell lines
- Absolute increase in RCM
- Normal oxygen saturation
- Splenomegaly
- Recommended treatment is phlebotomy
- Thrombosis and hemorrhage

## Table 12.4 Peripheral Blood and Bone Marrow Findings in the Three Phases of CML

| | Chronic Phase | Acceleratsed Phase | Blast Phase |
|---|---|---|---|
| *Peripheral blood* | Leukocytosis with the presence of neutrophils in all stages of maturation<br>Blasts >2%<br>Increased basophils<br>Increased eosinophils<br>Thrombocytosis<br>Mild anemia<br>NRBs | Increase in promyelocytes<br>Blasts increased<br>Basophils >20%<br>Increase in circulation NRBs Erythrocytes<br>Persistent thrombocytopenia<br>Anemia | Blasts >20%<br>Increase in promyelocytes<br>Increase in basophils and eosinophils<br>Thrombocytopenia |
| *Bone marrow* | Hyperplasia myeloid<br>Blasts <5%<br>M:E ratio 10:1<br>Increased immature forms of basophils<br>Reduced erythrocytes<br>Increased megakaryocytes | Dysplasia<br>Blasts >5% <20<br>Left shift of mature neutrophils<br>Increased basophils<br>Megakaryocytic proliferation in sheets and clusters<br>Fibrosis | Blasts >20%<br>Large clusters of blasts<br>Increased fibrosis<br>Marked dysplasia of all three cell lines |

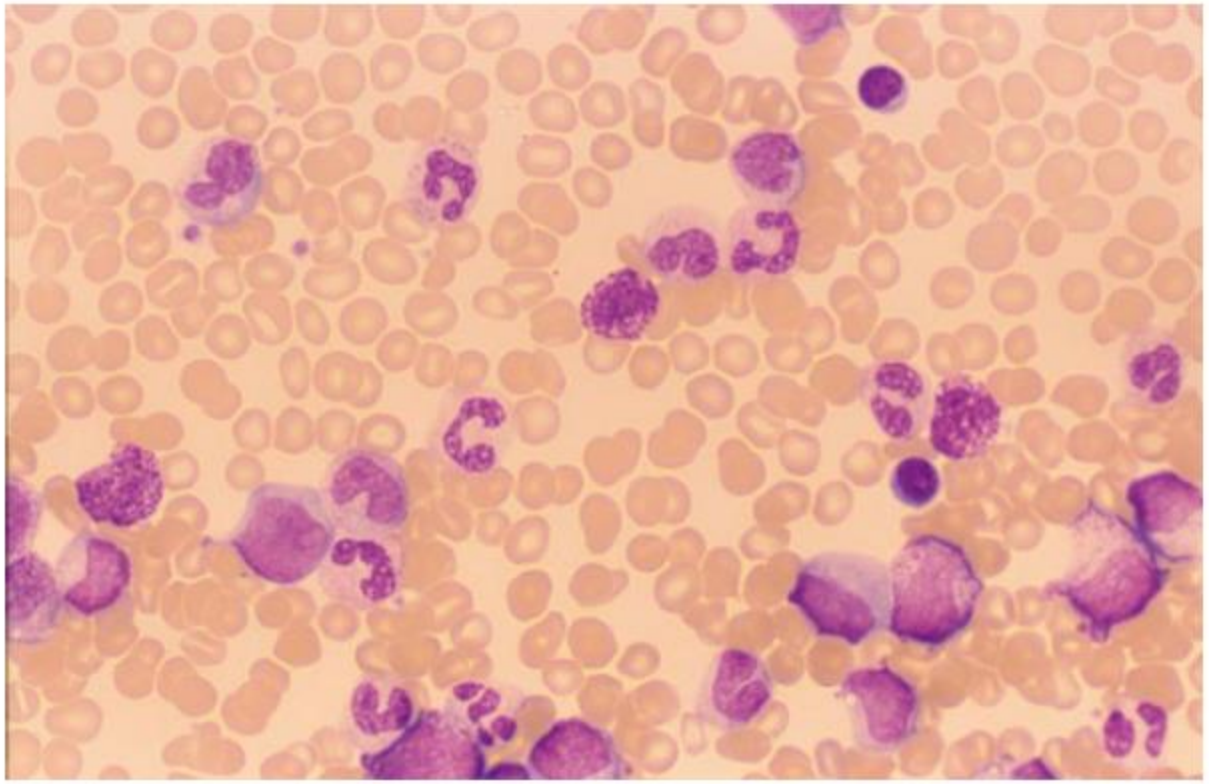


**Figure 14–1 Chronic myelogenous leukemia blood smear.** All stages of granulocyte maturation are present, with a predominance of mature forms; several basophils are present.

## Characteristics of Atypical Chronic Myelogenous Leukemia

- Median age: 60s
- Slight male predominance
- Monocytosis: 3–10% of WBC
- Dysplastic changes
- No basophilia
- Anemia and thrombocytopenia common
- Splenomegaly mild or absent
- No Philadelphia chromosome or *bcr/abl* rearrangement
- Short survival

## Characteristics of Juvenile Myelomonocytic Leukemia

- Age below 4 years
- Slight male predominance
- Fever
- Hepatosplenomegaly and lymphadenopathy
- Skin rashes
- Leukocytosis 20,000–30,000/μL with monocytosis >1,000/μL
- Anemia and thrombocytopenia
- Fetal erythropoiesis: increased Hb F, decreased Hb $A_2$
- Associated with neurofibromatosis type 1

## Characteristics of Chronic Myelomonocytic Leukemia

Older age group (median ~60–70 years)

Males > females

Monocytosis >1,000/μL in blood; >5% monocytes in bone marrow

Myelodysplastic changes

Variable WBC count: decreased to increased

Hepatosplenomegaly in ~25%

Variable clinical course

Transformation to AML in ~15%

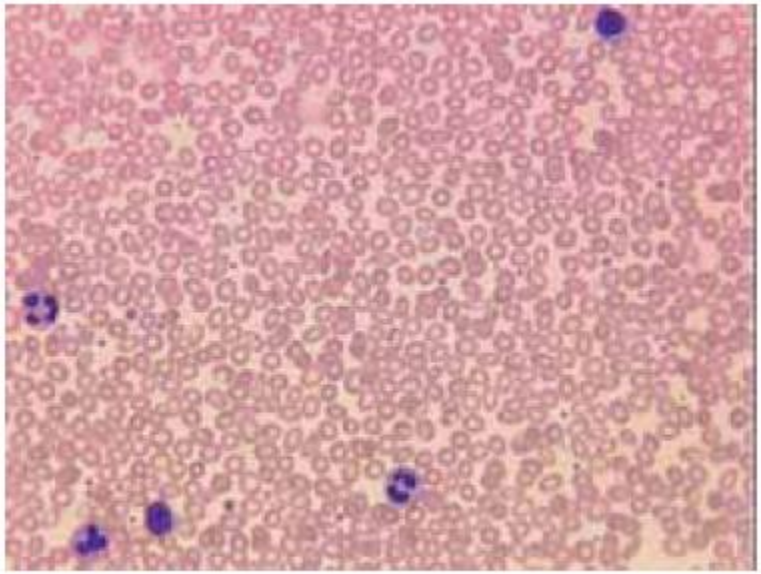


Figure 12.3 Increased RBCs in PV.

**Table 12.7 Causes of Secondary Erythrocytosis**

- Hypertension
- Arterial hypoxemia
- Impaired tissue oxygen delivery
- Smoking
- Renal lesions
- Renal disease
- Endocrine lesions
- Drugs
- Alcohol
- Hepatic lesions

*Table 14–8*

## Causes of Bone Marrow Fibrosis

| Neoplastic Causes | Non-neoplastic Causes |
|---|---|
| Chronic myeloproliferative disorders:<br>• Idiopathic myelofibrosis (IM)<br>• Chronic myelogenous leukemia (CML)<br>• Polycythemia vera (p. vera) | Granulomatous diseases:<br>• Mycobacterial infections<br>• Fungal infections<br>• Sarcoidosis |
| Acute megakaryoblastic leukemia (FAB-M7) | Paget's disease of bone |
| Myelodysplasia with myelofibrosis | Hypoparathyroidism |
| Hairy cell leukemia | Hyperparathyroidism |
| Acute lymphoblastic leukemia | Renal osteodystrophy |
| Multiple myeloma | Osteoporosis |
| Metastatic carcinoma | Vitamin D deficiency |
| Systemic mastocytosis | Autoimmune diseases:<br>• Systemic lupus erythematosus (SLE)<br>• Systemic sclerosis |

Adapted from Lee RG, Foerster J, Lukons J, et al, editors. Wintrobes's clinical hematology, 10th ed. Baltimore: Williams & Wilkins, 1999. p. 2391.

## Table 12.8 Diagnostic Criteria for Polycythemia Vera

| | |
|---|---|
| A1 | Elevated RCM >25% above mean normal predicated<br>Hgb >18.5 g/dL in men or 16.5 g/dL in women |
| A2 | No cause or absence of secondary erythrocytosis |
| A3 | Splenomegaly |
| A4 | Prescence of JAK2 V617 F mutation or other cytogenetic abnormalities in hemopoietic cells |
| A5 | Endogenous erythroid colony formation in vitro |
| B1 | Thrombocytosis >400 × $10^9$/L |
| B2 | WBC >12 × $10^9$/L |
| B3 | Bone marrow biopsy presenting with panmyelosis with prominent and megakaryocytic proliferation |
| B4 | Low serum erythropoietin levels |

## Table 12.9 Key Facts of Myelofibrosis

- Leukoerythroblastosis
- Extramedullary hematopoiesis
- Fibrosis of the bone marrow/reticulin silver stain
- Teardrop RBCs
- Absence of the Philadelphia chromosome
- Hepatosplenomegaly

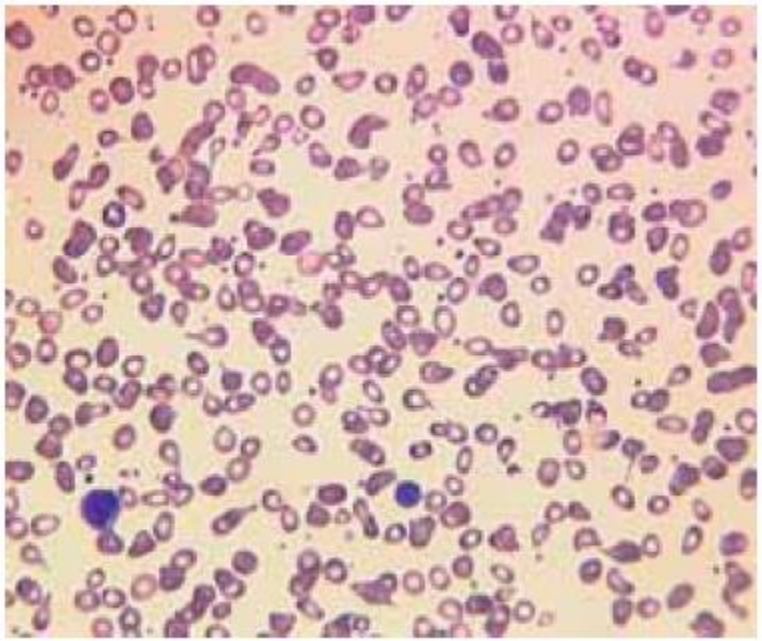


Figure 12.4 Teardrop RBCs in MMM.

## Table 12.10 Diagnostic Criteria for Myelofibrosis

| | |
|---|---|
| *Clinical Criteria* | |
| A1 | No preceding or allied subtype of CMPDs |
| A2 | Early clinical stages<br>Normal hemoglobin<br>Slight or moderate splenomegaly<br>Thrombocythemia platelets >400 × $10^9$/L |
| A3 | Intermediate clinical stage<br>Anemia<br>Definitive leukoerythroblastic blood picture/teardrop RBCs<br>Splenomegaly<br>No advance signs |
| A4 | Advanced clinical stage<br>Anemia<br>One or more adverse signs |
| *Pathological Criteria* | |
| B1 | Megakaryocytic and granulocytic proliferation<br>Reduction RBC precursors<br>Abnormal giant-sized megakaryocytes |

## Table 12.11 Key Facts for Essential Thrombocythemia

- Marked thrombocytosis (platelet count >600 × $10^9$/L)
- Usually no fibrosis
- Neurological manifestations
- Abnormal platelet function
- Megakaryocyte fragments in both peripheral blood and bone marrow
- Absent Philadelphia chromosome

## Table 12.13 Diagnostic Criteria for Essential Thrombocythemia

| | |
|---|---|
| I. | Platelet count >600 × $10^9$/L |
| II. | Hematocrit <40 or normal RBC mass (males <36 mL/kg, females <32 mL/kg) |
| III. | Stainable iron in marrow or normal serum ferritin or normal RBC mean corpuscular volume |
| IV. | Absent Philadelphia chromosome or *BCR-ABL* gene rearrangement |
| V. | Collagen fibrosis of marrow<br>A. Absent or<br>B. <⅓ of biopsy involved and neither marked splenomegaly nor a leukoerythroblastic reaction |
| VI. | No cytogenetic or morphological evidence for a myelodysplastic syndrome |
| VII. | No cause for reactive thrombocytosis |

## Table 12.14 Differentiation of Myeloproliferative Disorders

| Laboratory Findings | Chronic Myelogenous Leukemia | Myelofibrosis With Myeloid Metaplasia | Polycythemia Vera | Essential Thrombocythemia |
|---|---|---|---|---|
| Hematocrit | Normal/decreased | Decreased | Marked increased | Normal/decreased |
| WBC | Marked neutrophilia with a shift to the left<br>Basophilia and eosinophilia | Increased<br>Left shift with myeloblasts (occ)<br>Basophilia and eosinophilia | Normal/increased<br>Leukocytosis with neutrophilia and basophilia | Normal/increased<br>Leukocytosis usually mild |
| RBC | Normal<br>Few nRBCs | Teardrop reticulocytosis<br>nRBCs | Normal morphology as disease progresses; iron defi- | Normal morphology and maturation |
| Immature granulocytes | Increased | Increased | Absent or shift | Rare |
| LAP | Decreased | Normal/increased | Increased | Normal |

| Laboratory Findings | Chronic Myelogenous Leukemia | Myelofibrosis With Myeloid Metaplasia | Polycythemia Vera | Essential Thrombocythemia |
|---|---|---|---|---|
| Platelets | Normal/increased<br>Enlarged and fragments | Normal/decreased/increased<br>Giant and abnormal megakaryocytes present | Increased | Increased<br>Platelet count >600,000/μL<br>Giant size<br>Bizarre shapes<br>Micromegakaryocytes and megakaryocytic fragments |
| Ph chromosome | Present | Absent | Absent | Absent |
| Spleen | Normal/increased | Increased | Increased | Normal/increased |
| Bone marrow | Hypercellular predominantly granulocytic<br>decreased iron stores | Increased fibrosis<br>Megakaryocytic hyperplasia<br>RBCs and WBCs usually normal<br>Bone marrow aspirate DRY TAP | Hypercellular moderate to severe<br>All three lines increased with normal maturation<br>Deceased iron stores | Hypercellular mild to moderate<br>Megakaryocytic hyperplasia<br>Clusters and sheets of megakaryocytes<br>Some marrow fibrosis |
| Diagnostic criteria | Complete rainbow of all stages of neutrophil maturation<br>Less than 5% blasts in peripheral blood<br>Ph chromosome present in 90% to 95% of cases<br>Three clinical phases:<br>Chronic<br>Accelerated<br>Blast | Leukoerythroblastic picture with teardrop RBCs<br>Fibrotic marrow as disease progresses<br>Enlarged spleen | Excessive RBC production<br>Increased red cell volume, normal $O_2$ saturation, all three lines increased<br>Enlarged spleen | Platelet count greater than 600,000/μL with no known cause for reactive thrombocytosis<br>Complications of thrombosis and hemorrhage |

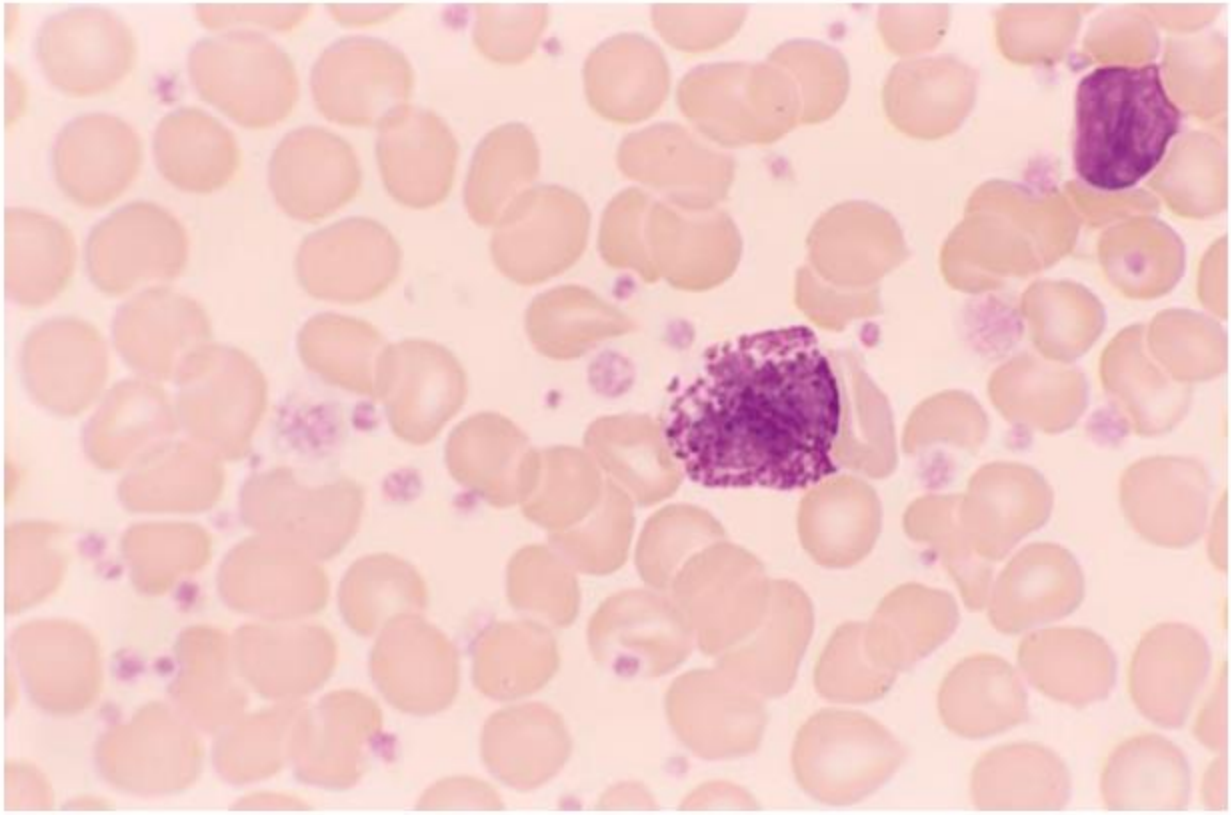


**Figure 14–2 Primary thrombocythemia blood smear.** Platelets are markedly increased; a basophils is present in the center. The cell in the top right is a megakaryocyte nuclear fragment.

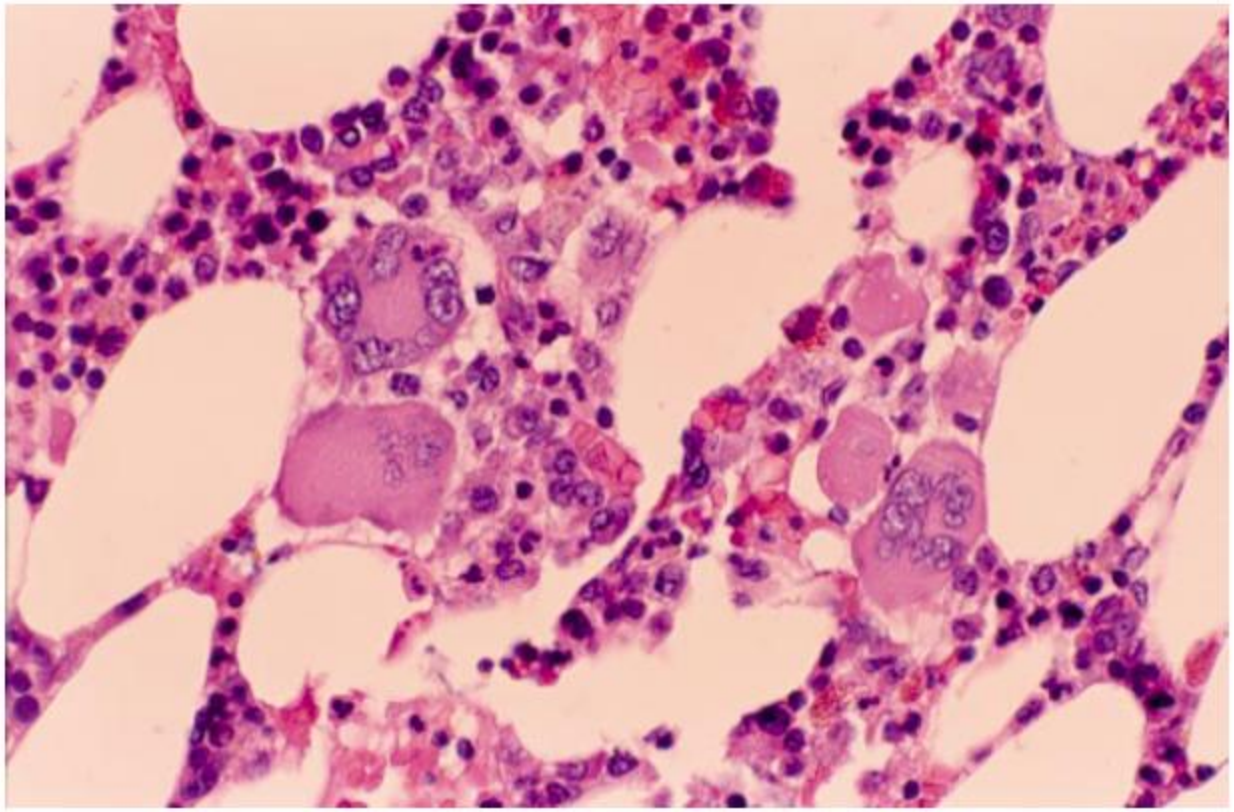


**Figure 14–3 Primary thrombocythemia bone marrow biopsy.** A cluster of megakaryocytes is present.

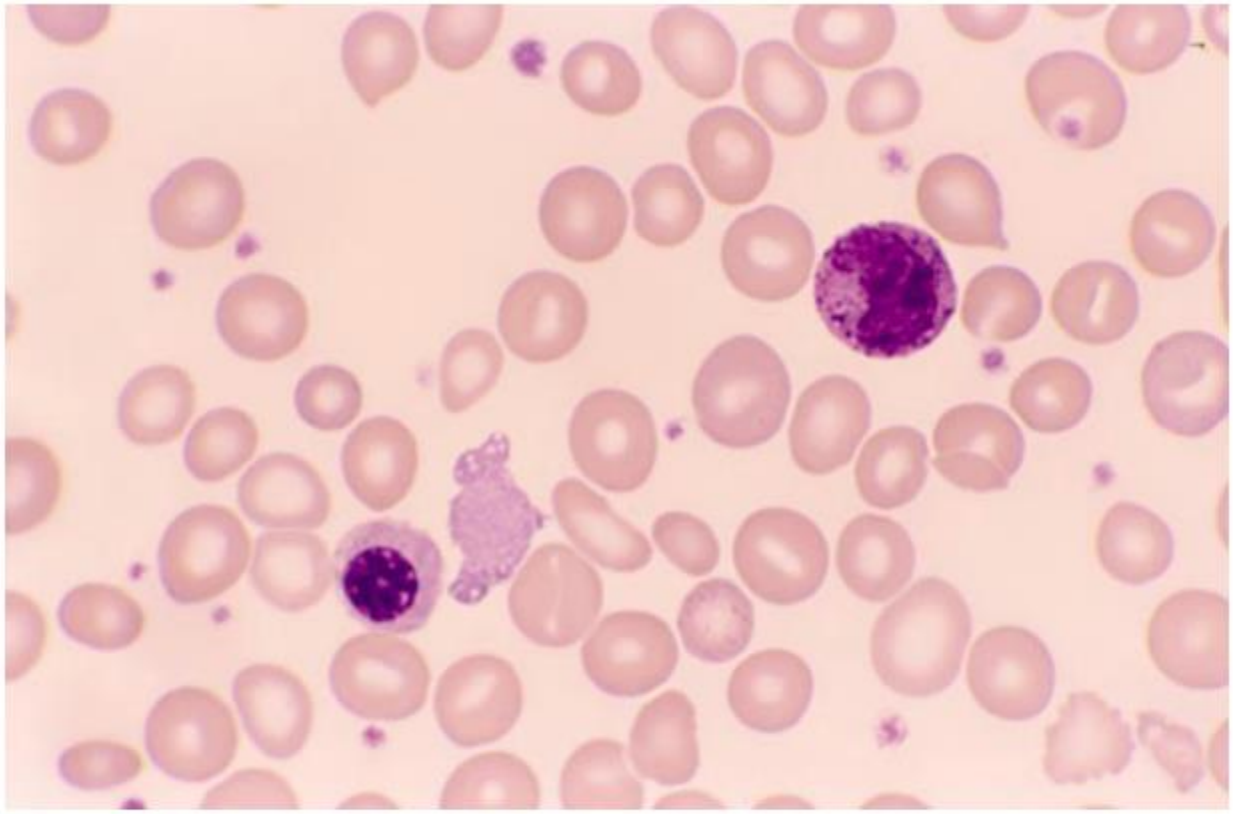


**Figure 14–4 Idiopathic myelofibrosis blood smear.** Nucleated erythrocyte, bizarre platelet, and basophil are seen.

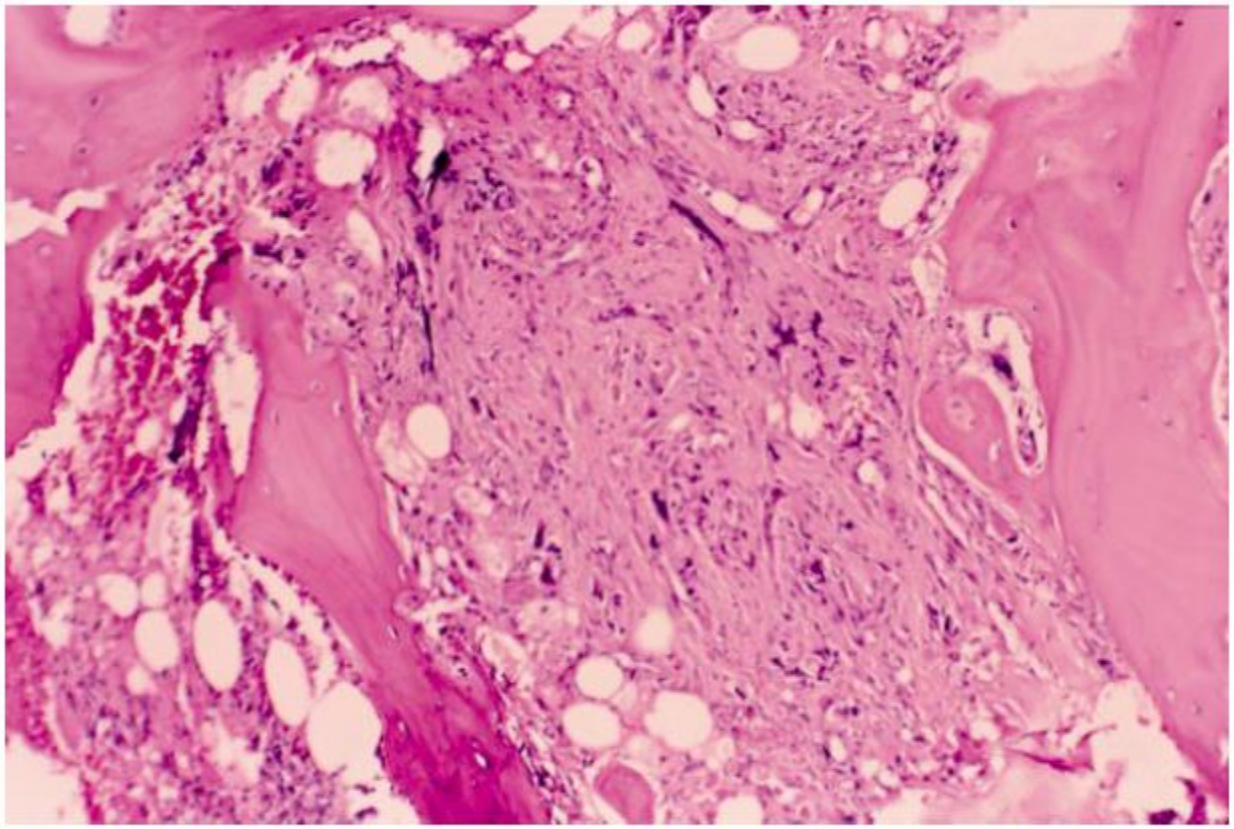


**Figure 14–5 Idiopathic myelofibrosis bone marrow biopsy (hematoxylin and eosin stain).** The solid pink area represents dense fibrosis.

*The chronic lymphocytic* leukemias are a heterogeneous group of conditions characterized by an *increased number of small, mature-appearing lymphocytes in the blood*. By far the most common is a proliferation of small B cells that express the T cell–associated antigen CD5; the term chronic lymphocytic leukemia (**CLL**) refers to this entity unless specified otherwise. This type of CLL is closely related to B-cell *diffuse small lymphocytic lymphoma* (**SLL**). Less common B-cell CLLs include *hairy cell leukemia* (**HCL**) and B-cell *prolymphocytic leukemia* (**B-PLL**). Patients with non-Hodgkin's lymphomas may develop lymphocytosis, and occasionally lymphocytosis is the presenting feature of the lymphoma.

Mature T-cell lymphoproliferations occur, but these are rare. They include *T-prolymphocytic leukemia* (**T-PLL**) and *large granular lymphocytic leukemia* (*T-γ lymphocytosis*). A form of T-cell proliferation designated *adult T-cell leukemia/lymphoma* (**ATL/L**) has been linked to the human T-cell lymphocytotrophic virus I (HTLV-I). It is common in parts of the Far East, but rare in the United States. *Sézary syndrome* (SS) is a proliferation of T helper cells, related to a cutaneous T-cell lymphoma (mycosis fungoides).

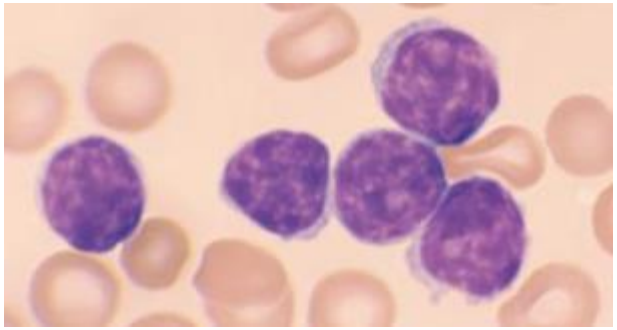


**Table 13.1 Modified Rai Staging for Chronic Lymphocytic Leukemia**

| Staging | Lymphocytes | Lymph Nodes | Spleen | Platelet Count | Survival |
|---|---|---|---|---|---|
| 0 | Increased | | | | 12.5 years |
| I | Increased | Enlarged | | | 8.5 years |
| II | Increased | Enlarged/some | Enlarged | | 6 years |
| III | Increased | Enlarged/some | Enlarged | | 1.5 years |
| IV | Increased | | | Decreased | 1.5 years |

## Binet Staging System for CLL

| Stage | ≥3 Lymphoid Sites | Hemoglobin <10 g/dL +/or Platelets <100,000/μL |
|---|---|---|
| A | – | – |
| B | + | – |
| C | +/– | + |

A = lowest stage; B = intermediate; C = highest.

**Table 25.1** Prognostic features of CLL.

| | Favourable | Unfavourable |
|---|---|---|
| Sex | Female | Male |
| Stage | A | B,C |
| Lymphocyte doubling time | >1 year | <6 months |
| ZAP-70 | Negative | Positive |
| Somatic mutation | Mutated | Germline |
| Cytogenetics | 13q deletions | Trisomy 12, p53 deletions |

*Table 16–6*

## Features of Hairy Cell Leukemia

| |
|---|
| Circulating lymphocytes with filamentous cytoplasmic projections (hairy cells) |
| Splenomegaly with or without hepatomegaly |
| Neutropenia and monocytopenia |
| Positive tartrate-resistant acid phosphatase (**TRAP**) stain |
| Expression of CD11c, CD25, and CD103; absence of CD5 |

**Table 13.2 CD Markers in Hairy Cell Leukemia**

- CD19
- CD20
- CD22
- CD11c—membrane adhesion
- CD25
- CD103

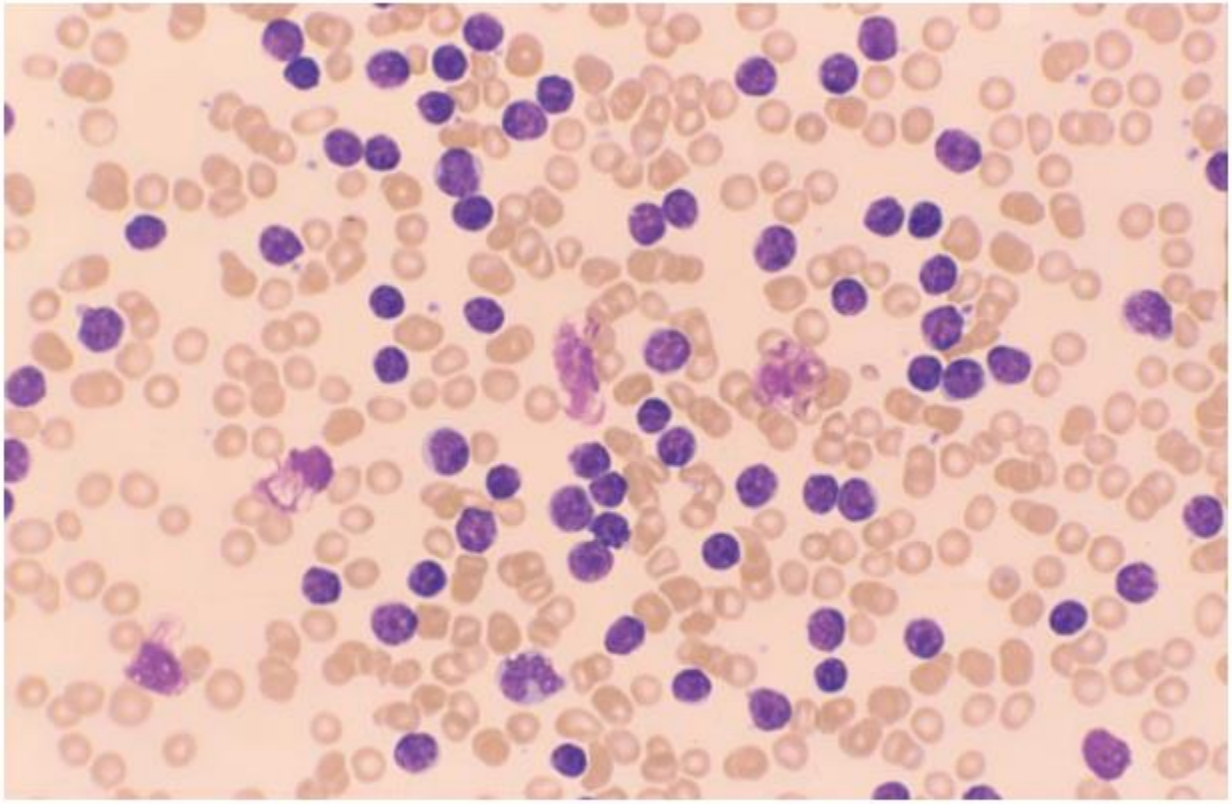


**Figure 16–1 B-cell chronic lymphocytic leukemia, low power.** Lymphocytosis of small mature-appearing lymphocytes. Numerous "smudge" cells are present.

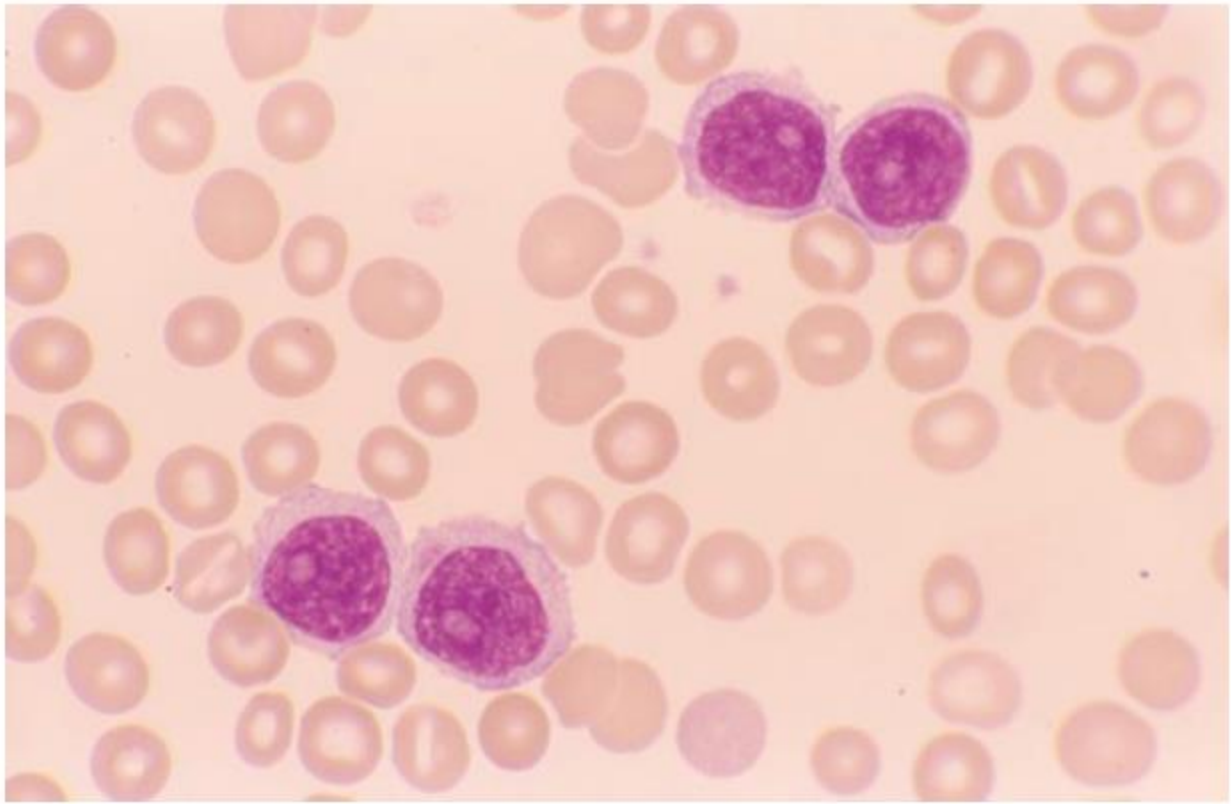


**Figure 16–5** Prolymphocytic leukemia.

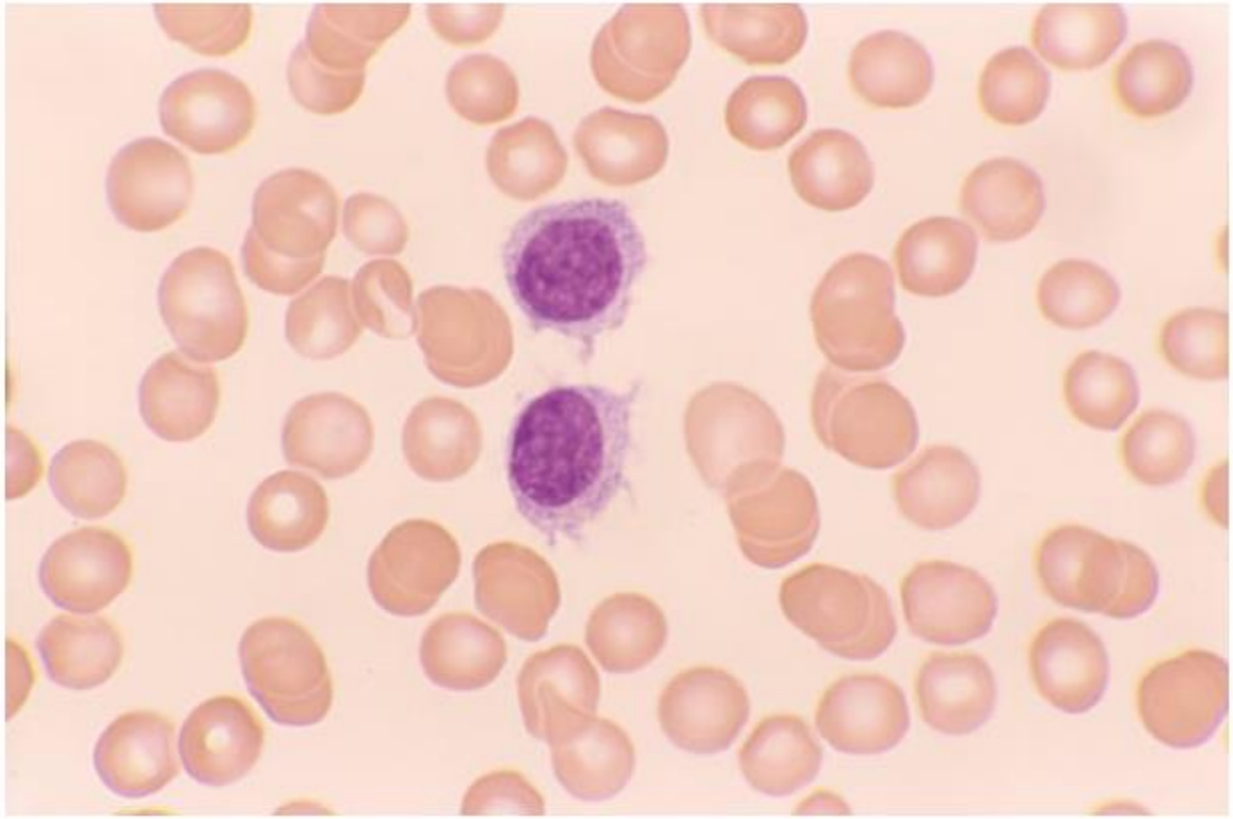


**Figure 16–3 Hairy cell leukemia.** Lymphocytes with filamentous cytoplasmic projections.

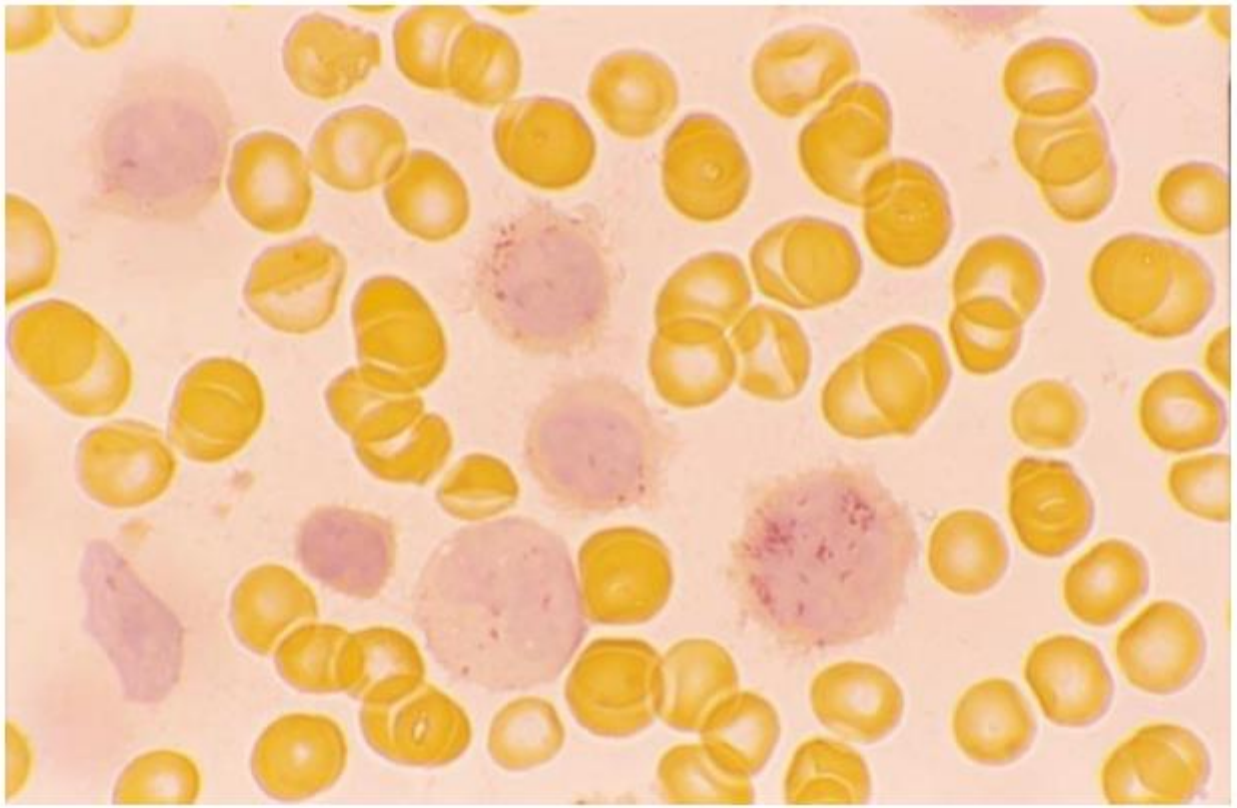


**Figure 16–4 Hairy cell leukemia, TRAP stain.** Acid phosphatase reaction after incubation with tartaric acid. Granular staining is seen in the lymphocytes.

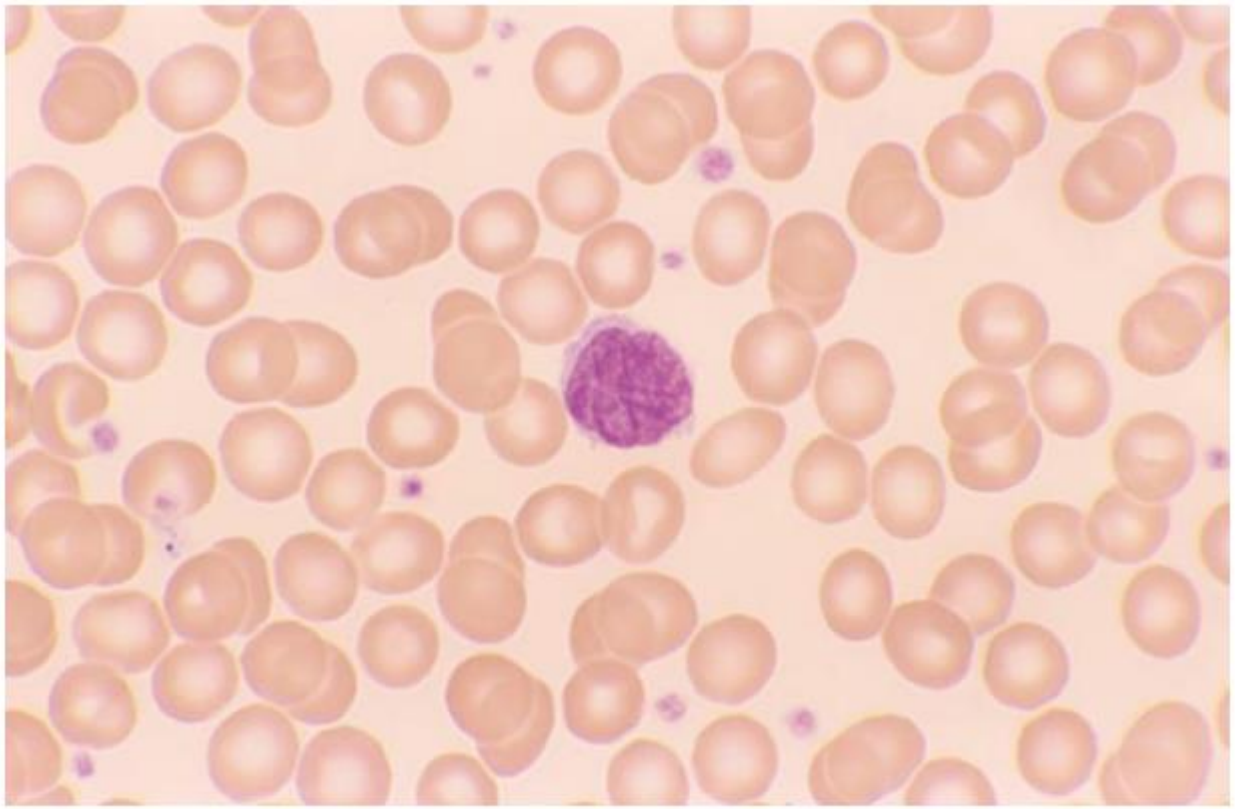


**Figure 16–6 Sézary cell.** Note the prominent nuclear grooves.

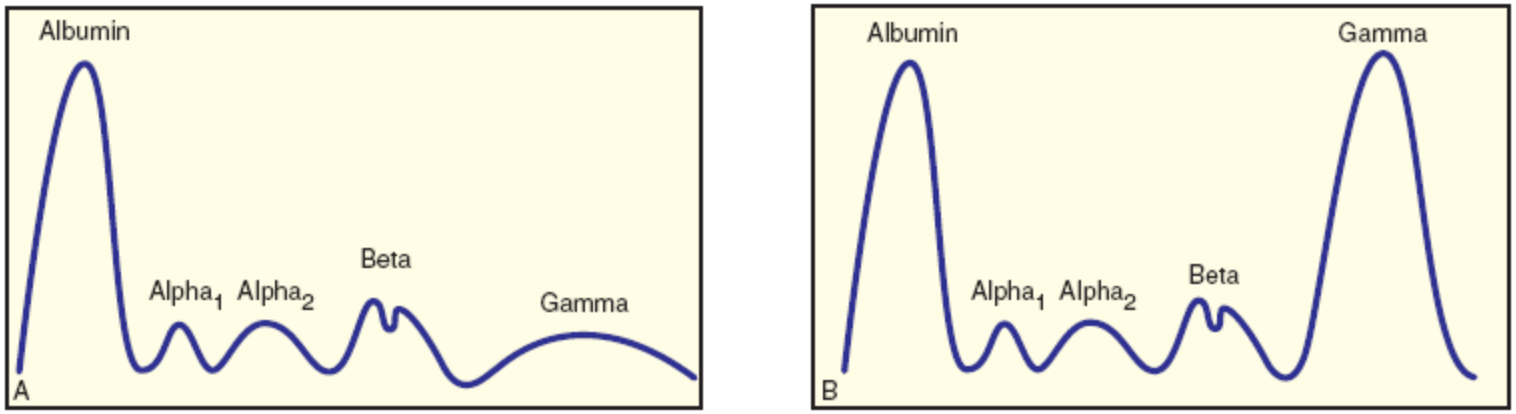



**Figure 13.6** Serum protein electrophoresis showing patterns of (*A*) normal serum and (*B*) serum from patient with multiple myeloma; note the monoclonal spike in the gamma

## *Pathophysiology in Multiple Myeloma*

Disease and clinical symptoms in multiple myeloma follow along three distinct pathways:

1. Acceleration of plasma cells in the bone marrow
2. Activation of bone resorption factors or osteoclasts
3. Production of an abnormal monoclonal protein

**Table 13.5 A Simplified list of Chromosomal Aberrations in Multiple Myeloma**

- 13q14 deletions
- 14q32
- t(11:14)(q13:q32)
- t(4:14)

**Table 13.6 Laboratory Findings of Multiple Myeloma**

- Pancytopenia
- N/N anemia
- ↑ ESR
- ↑ Calcium
- ↑ Urine protein
- ↑ Uric acid
- Abnormal serum electrophoresis

**Figure 18–1 Multiple myeloma skull radiograph.** Multiple osteolytic lesions are present.

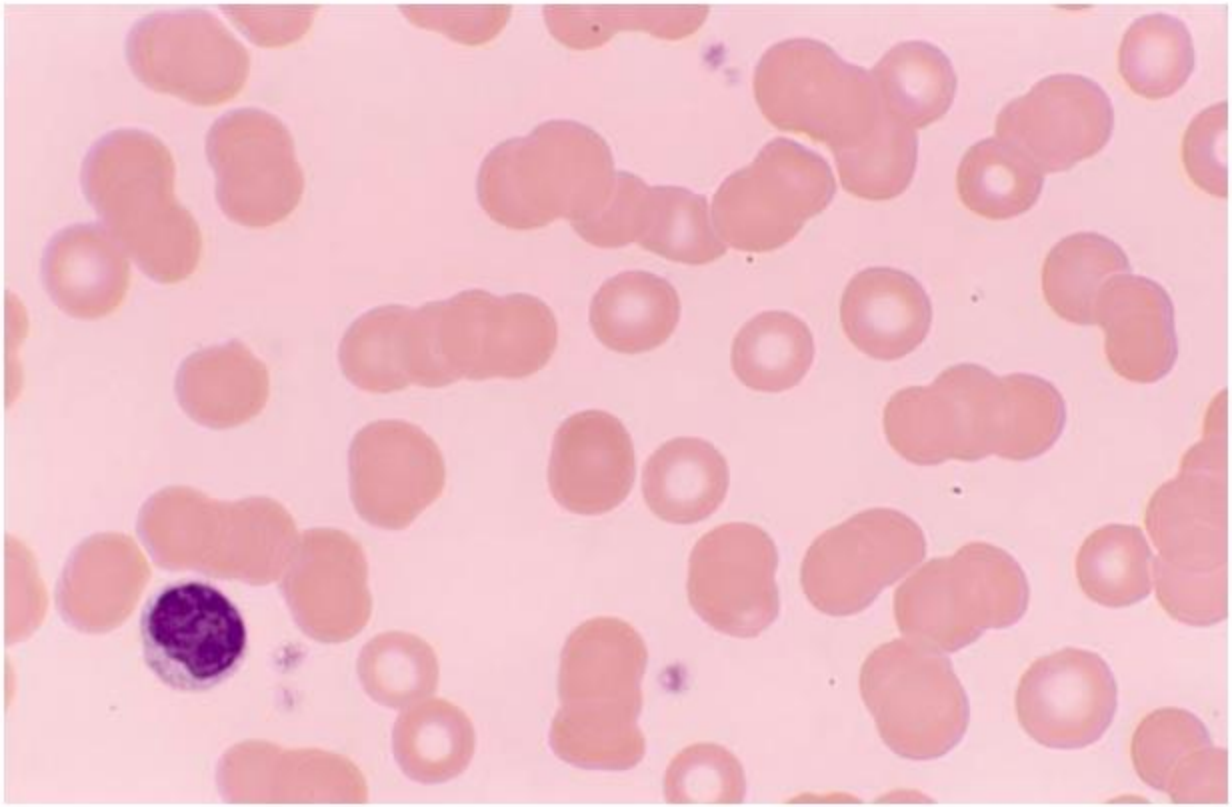


**Figure 18–4 Multiple myeloma blood smear.** Rouleaux formation.

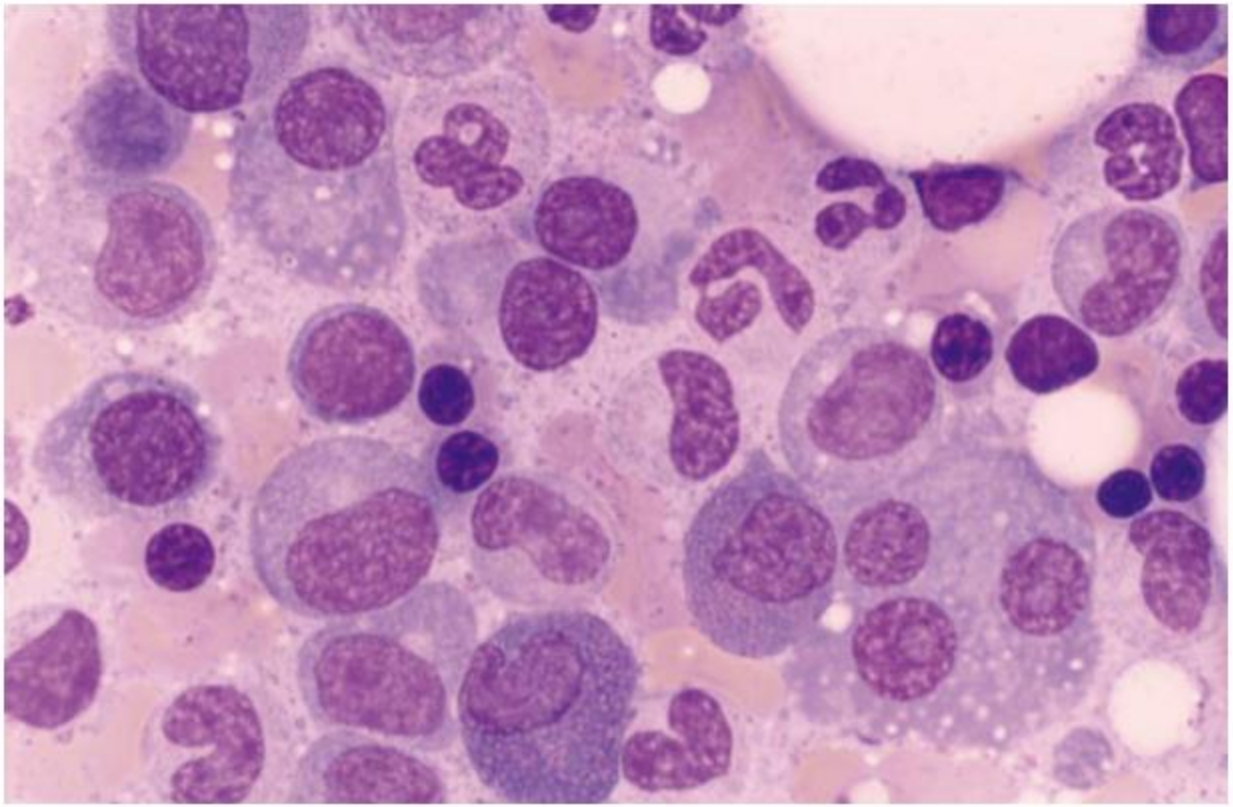


**Figure 18–3 Multiple myeloma bone marrow aspirate.** Numerous plasma cells, many of which have prominent nucleoli (normal plasma cells lack nucleoli), are present.

**Table 32–18** Diagnostic Criteria for Plasma Cell Myeloma and for Monoclonal Gammopathy of Undetermined Significance (MGUS), Indolent and Smoldering Myeloma

| Major criteria for plasma cell myeloma | Minor criteria for plasma cell myeloma |
|---|---|
| A. Marrow plasmacytosis (> 30%) | 1. Marrow plasmacytosis (10–30%) |
| B. Plasmacytoma on biopsy | 2. M-component: present but less than for C |
| C. M-component<br>Serum: IgG > 3.5 g/dL, IgA > 2 g/dL<br>Urine: > 1 g/24 h of Bence-Jones (BJ) protein | 3. Lytic bone lesions<br>4. Reduced normal immunoglobulins (< 50% normal):<br>IgG < 600 mg/dL, IgA < 100 mg/dL, IgM < 50 mg/dL |

**Myeloma**

One major and one minor criterion or three minor criteria which must include 1 and 2, in symptomatic patient

**MGUS**

M-component present, but less than myeloma levels

Marrow plasmacytosis < 10%

No lytic bone lesions

No myeloma-related symptoms

**Smoldering myeloma**

Same as MGUS except:

Serum M-component at myelomas levels

Marrow plasmacytosis 10–30%

**Indolent myelomas**

Same as myeloma except:

M-component: IgG < 7 g/dL, IgA < 5 g/dL

Rare bone lesions (≤ 3 lytic lesions), without compression fractures

Normal hemoglobin, serum calcium and creatinine

No infections

## Table 13.7 Overview of Major Malignant Lymphoproliferative Disorders

| | CLL | HCL | HL | NHL | MM | WM |
|---|---|---|---|---|---|---|
| Predominant cell type* | Mature lymphocyte | Hairy cell | Reed-Sternberg cell (in node) | Lymphocyte<br>Lymphocyte variations | Plasma cells in marrow | Plasmacytoid lymphs |
| Main symptoms | Fatigue<br>Weight loss | Infections<br>Bleeding | Enlarged lymph node | Painless, enlarged lymph node | Bone pain, thirst, fatigue | Bleeding, lymphadenopathy<br>Dizziness, blurred vision |
| Significant lab findings | ↑↑↑ WBC<br>Peripheral smear shows 90% lymphs | TRAP +<br>Pancytopenia | Variable presentations | Variable presentations | ↑↑ Calcium, hyperviscosity (↑ ESR), monoclonal gammopathy (IgG-M spike), rouleaux | Monoclonal gammopathy (Ig M), hyperviscosity (ESR ↑)<br>Rouleaux |
| Organ involvement | Enlarged lymph nodes | ↑↑↑ Spleen | Possibly extranodal sites | Possible extranodal sites | Kidneys<br>Bone marrow | Kidneys<br>Bone marrow |
| Survival rate | Variable | Good | Good | Poor | Variable | Poor |
| Immunological markers | CD15, CD19, CD20, CD22 | CD19, CD20, CD22, CD11c, D25, CD103 | CD15 | None | CD38 | CD19, CD20, CD22 |

## Table 14.3 Factors Indicating Progression to Leukemia in MDS

- Disease is stable if there is little increase in marrow blast count and the original karyotype is unchanged.
- Progressive rise in blast count usually indicates transition to acute leukemia.
- Sudden change in karyotype that may progress into acute leukemia.
- Abnormal karyotype develops without subsequent increase in blasts; acute leukemia may or may not develop.

**TABLE 12-4 MANIFESTATIONS OF DYSPLASIA IN MYELODYSPLASTIC SYNDROMES**

| *Cell Lineage* | *Bone Marrow* | *Peripheral Blood* |
|---|---|---|
| Erythroid | • Prominent erythroblast nucleoli<br>• Irregular normoblast nuclear contour<br>• Multiple normoblast nuclei<br>• Cytoplasmic outpouches in normoblasts<br>• Normoblast cytoplasmic vacuoles<br>• Delayed normoblast hemoglobinization<br>• Ringed sideroblasts<br>• Karyorrhexis<br>• Excessive numbers of myeloblasts | • Basophilic stippling<br>• Nucleated red blood cells<br>• Macroerythrocytes<br>• Howell-Jolly bodies |
| Myeloid | • Prominent nucleoli in myeloblasts and promyelocytes<br>• Irregular nuclear contour in myeloblasts and promyelocytes<br>• Few specific granules in metamyelocytes<br>• Mixed eosinophilic and basophilic granules in cells at the myelocyte and metamyelocyte stages<br>• Karyorrhexis | • Pseudo-Pelger-Huet cells<br>• Hypogranulated neutrophils |
| Megakaryocytic | • Micro-megakaryocytes | • Giant platelets |

Table 32–13 Key Features of the Major Myelodysplastic Syndromes

| Disorder | Demographics | Laboratory features, morphology | Cytogenetics | Prognosis |
|---|---|---|---|---|
| Refractory anemia (RA) | Over age 50 | PB with anemia, reticulocytopenia, blasts < 1%. BM with erythroid hyperplasia and/or dyspoiesis, < 5% blasts. | Rare abnormalities | Good, > 5 years; 6% progress to AML |
| Refractory anemia with ringed sideroblasts (RARS) | Over age 50 | Similar to RA, ≥ 15% ringed sideroblasts in BM | Rare abnormalities | Good, > 5 years, with ≤ 2% to AML |
| Refractory cytopenia with multilineage dysplasia (RCMD) | Over age 50 | PB with cytopenias of ≥ 2 cell lines, < 1% blasts, < $1 \times 10^9$/L monocytes. BM with dysplasia of ≥ 10% of precursors of ≥ 2 cell lines, < 5% blasts | +8, –7, del(7q), –5, others in up to 50% | 33 months, 11% to AML |
| Refractory anemia with excess blasts (RAEB) | Over age 50 | RAEB-1: PB with cytopenias of ≥ 2 cell lines, < 5% blasts, < $1 \times 10^9$/L monocytes. BM with hypercellularity, dyspoiesis, 5–9% blasts without Auer rods | +8, –5, del(5q), –7, del(7q), del(20q) | RAEB-1: < 2 years with 25% to AML |
| | | RAEB-2: Similar to RAEB-1, but also PB with > 5% blasts, or 10–19% BM blasts, or Auer rods | | RAEB-2: < 2 years with 33% to AML |
| 5q- Syndrome | Middle-aged–older females | PB with thrombocytosis, < 5% blasts. BM with increased, hypolobated megakaryocytes, < 5% blasts | 5q- is sole abnormality | Good |

PB = peripheral blood; BM = bone marrow.

Cytogenetic Abnormalities in Myelodysplastic Syndromes

| *Alteration* | *Prognostic significance*[a] |
|---|---|
| 5q–[b] | Favorable |
| –5, –7, or 7q– | Adverse |
| +8 | Adverse |
| 20q– | Neutral |
| 11q– | Neutral |
| –Y | Neutral |
| –17 or 17p– | Adverse |
| Translocation of 3q26 | Adverse |
| Translocation of 11q23 | Adverse |
| Multiple | Adverse |

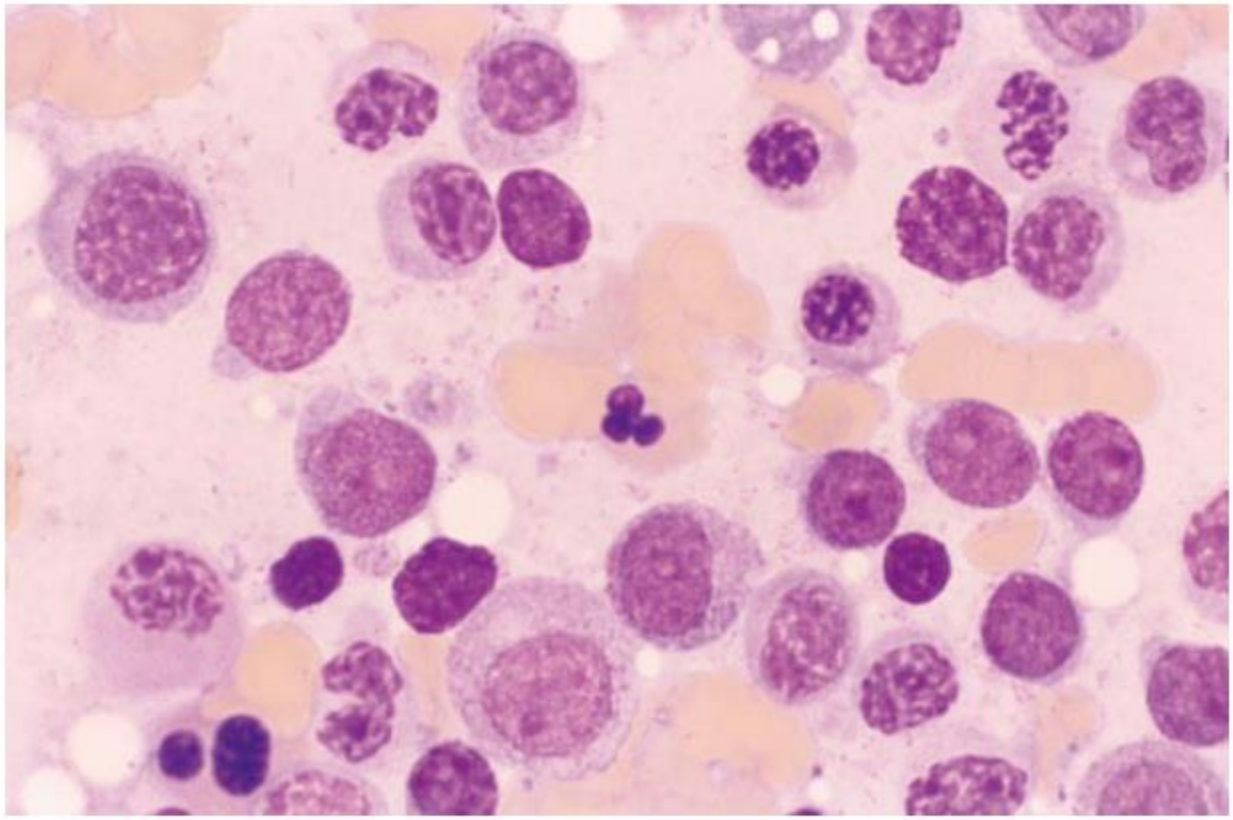


**Figure 15–2 Myelodysplasia bone marrow aspirate.** Abnormal erythroid precursor with multilobated nucleus.

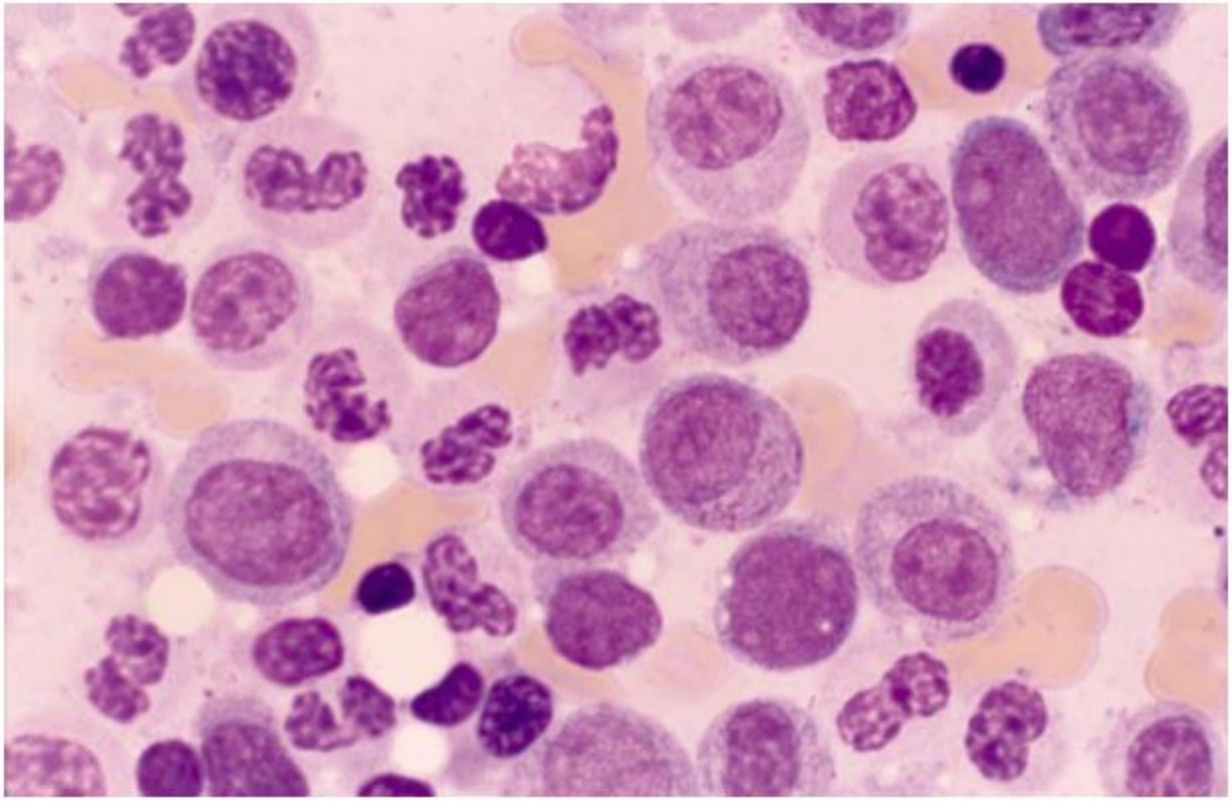


**Figure 15–3 Myelodysplasia bone marrow aspirate.** Hypogranular hyposegmented neutrophils.

*Table 17–1*

## Hodgkin's Disease versus the Non-Hodgkin's Lymphomas

| Hodgkin's Disease | Non-Hodgkin's Lymphomas |
|---|---|
| Orderly contiguous spread | Noncontiguous, widely disseminated spread |
| Predominant central and axial lymph node involvement; rare peripheral node involvement | Frequent involvement of both central and axial and peripheral lymph nodes |
| Mesenteric nodes and Waldeyer's ring involved seldom or late | Frequent involvement of mesenteric nodes and Waldeyer's ring |
| Extranodal presentation rare | Extranodal presentation not uncommon |

Table 32–17 Key Features of the Major Mature B Cell Neoplasms

| Lymphoma | Demographics, clinical and laboratory presentation | Morphology | Cell surface markers: Positive | Cell surface markers: Negative | Cytogenetics |
|---|---|---|---|---|---|
| CLL/SLL | M > F, over 60 years. Insidious onset of fatigue, lymphadenopathy. WBC > 30K, anemia, thrombocytopenia, occasionally AIHA | Monomorphic, small lymphocytes with slight–moderate cytoplasm, condensed chromatin | CD5, 19, 20, 23, 79a, dim sIg | CD10, 22, Bcl-6 | +12, del(13q14), del(11q22-23), Ig rearrangement |
| B cell PLL | M >> F, mean age 65 years. Massive splenomegaly, minimal lymphadenopathy, WBC > 100K | Prolymphocytes ≥ 55% with large vesicular nucleus, condensed chromatin, moderate cytoplasm | CD19, 20, bright sIg | Often CD5, 23 negative | del(11q23), del(13q14), Ig rearrangement |
| Hairy cell leukemia | M > F, median age 50 years. Insidious onset with splenomegaly, monocytopenia | Medium-sized cells with round–oval nuclei, reticular chromatin, frayed cytoplasmic borders | CD 19, 20, 22, 79a, 103, 25, 11c | CD5, 10, 23 | Ig rearrangement |
| Lymphoplasmacytic lymphoma | M = F, mean age 63. BM, nodal and splenic involvement, and frequent IgM paraprotein with hyperviscosity (WM) causing decreased visual acuity, risk for CVA, neuropathies | Plasmacytoid lymphocytes and plasma cells with PAS-positive inclusions (Dutcher bodies) | CD19, 20, 22, 38, 79a, bright sIgM, cIgM | CD5, 10, 23 | t(9;14)(p13;q32) |
| Alpha heavy chain disease | Younger adults in poorer Mediterranean communities with malabsorption, diarrhea | Lymphoplasmacytic infiltrate of intestinal mucosa | NA | NA | NA |
| MALT lymphoma | F > M, median age 61. Indolent course involving stomach, other GI sites. Associated with antecedent autoimmune disease (SS, Hashimoto's) or *H. pylori* infection | Lymphoepithelial lesions with small lymphocytes, centrocytes, monocytoid lymphocytes and reactive germinal centers | CD19, 20, 22, 79a, sIg, bcl-2 | CD5, 10, 23, bcl-6 | +3, t(11;18)(q21;q21) |
| Follicular lymphoma | F > M, median age 59 years. Peripheral lymphadenopathy dominates, with central adenopathy, BM and splenic involvement frequent | Follicle-like structures with small, cleaved lymphocytes and varying numbers of larger centroblasts which allow for cytologic grading | CD19, 20, 22, 23, 79a, 10, bcl-2, bcl-6 | CD5, 43 | t(14;18)(q32;q21) |

**Table 32–17** Key Features of the Major Mature B Cell Neoplasms

| Lymphoma | Demographics, clinical and laboratory presentation | Morphology | Cell surface markers: Positive | Cell surface markers: Negative | Cytogenetics |
|---|---|---|---|---|---|
| Mantle cell lymphoma | M > F, median age 60 years. Lymphadenopathy, marked splenomegaly, BM involvement, Aggressive course | Atrophic germinal centers, prominent mantle zones, monomorphic cells with small–medium nuclei | CD19, 20, 22, 5, 43, bcl-2, cyclin D1 | CD10, 23, bcl-6 | t(11;14)(q13;q32) |
| Diffuse large B cell lymphoma | M > F, all ages, associated with HIV. Nodal and extranodal sites, CNS. Aggressive course | Diffuse infiltrate of variably large B cells, sometimes with centroblastic or *immunoblastic morphology* | CDCd19, 20, 22, 79a, sIg. Occasionally CD30 (anaplastic variant) | CD5 (usually), 23 | t(14;18) in 20–30%, 3q27 abnormality in up to 30%, complex abnormality |
| Mediastinal large B cell lymphoma | F > M, young–middle-aged adults. Airway compression, superior vena cava syndrome | Sclerotic lesions with clear, multilobated or RS-like cells | CD45, 19, 20 | CD5, 10 | Ig rearrangement |
| Primary effusion lymphoma | Rare, associated with HHV-8 in immunosuppressed, younger male homosexuals. Pleural effusion | Immunoblastic or anaplastic cells | CD19, 20, 79a, often CD30, 38, 138 | sIg, cIg | Ig, occasionally TCR rearrangement |
| Burkitt lymphoma | 1. Endemic: children in Africa, jaw mass, M > F<br>2. Sporadic: children–young adults, worldwide, M > F, abdominal organs<br>3. Immunodeficiency-associated: HIV patients | Uniform cells with round–oval nuclei, multiple nucleoli, high mitotic rate | CD19, 2, 20, 79a, sIg, often CD10 | TdT | t(8;14)(q24;q32) |

WM = Waldenström's macroglobulinemia; PAS = periodic acid–Schiff; SS = Sjögren's syndrome; RS = Reed–Sternberg.

Table 32–20 Key Features of the Major Mature T and NK Cell Neoplasms

| Lymphoma | Demographics, clinical and laboratory presentation | Morphology | Cell Surface Markers: Positive | Cell Surface Markers: Negative | Gene Rearrangements |
|---|---|---|---|---|---|
| T cell PLL | M > F, median age 69 years. Lymphocytosis > $100 \times 10^3$, anemia, thrombocytopenia, HSM, skin lesions | Prolymphocyte with prominent nucleoli, perinuclear chromatin, abundant cytoplasm | CD7; CD4 (60%), CD4/8 (25%), CD8 (15%) | | TCRα-β, inv(14)(q11;q32) |
| LGL leukemia | Median age 63. Neutropenia causing infections, anemia, mild lymphocytosis, LGL > $2 \times 10^3$ | Moderately sized cell with condensed chromatin, abundant pale blue cytoplasm, azurophilic granules | CD3, 8, 57, TCRα-β | CD4 | TCRγ, β |
| | | | Some variants are CD4+ or CD4/8+ or CD4/8– | | |
| Aggressive NK cell leukemia | Asian teens–young adults. Constitutional symptoms, HSM, variable WBC | Variable, may resemble LGL cells or appear blastic | cCD3ε, 2, 56 | sCD3, 57 | Clonal episomal EBV, del(6)(q21;q25) |
| Adult T cell leukemia-lymphoma | Associated with HTLV-1, frequent in Japan, Caribbean, central Africa. Acute variant with skin, lymph node involvement, hypercalcemia | Moderately large, blastic cells with convoluted nuclei (floret cells), agranular, basophilic cytoplasm | CD 2, 3, 5, 25, often CD30 | CD4, 7 | TCR genes |
| Extranodal NK/T cell lymphoma, nasal type | M > F, Latin America and Asia. Massive nasopharyngeal destruction. EBV associated | Polymorphic lymphoid cells, often angiocentric or angioinvasive, with mucosal ulceration | CD2, 56, cCD3ε | CD4, 8, 5, 16, 56 | Clonal episomal EBV |
| Mycosis fungoides/Sézary syndrome (SS) | M >F, middle-age–older. Dermatitis progressing to ulcerated lesions. PB blood involvement in SS | Dermal band-like infiltrates of lymphocytes with cerebriform nuclei, microabscesses | CD2, 3, 4 | CD7, 8 | TCR genes |
| Primary cutaneous CD30-positive | M > F, adults–elderly. Limited to skin lesions | Polymorphic lymphoid cells, some anaplastic | CD4, 30 | Often CD2, 3, 5 | TCR genes ALK-negative |
| Anaplastic large cell lymphoma | M = F, teens, young adults. Peripheral, abdominal adenopathy, extranodal and BM involvement, frequent B symptoms | Pleomorphic large cells, wreath-like nuclei, multiple nucleoli, abundant cytoplasm | CD30 (cytoplasmic and Golgi), CD2, 4 | CD3, 5, 7, EBV | t(2;5)(p23;q35) Other variants involve 2p23 |

PLL = prolymphocytic leukemia; HSM = hepatosplenomegaly; LGL = large granular lymphocyte; EBV = Epstein–Barr virus; PB = peripheral blood ; BM = bone marrow.

Table 32-21 Key Features of Hodgkin Lymphomas

| Lymphoma | Demographics, clinical presentation | Morphology | Cell surface markers | Prognosis |
|---|---|---|---|---|
| Nodular, lymphocyte predominant | M > F, 30–50 years, with peripheral lymphadenopathy | L&H cells with large, convoluted nuclei, vesicular chromatin, prominent nucleoli (popcorn cells) loosely aggregated in nodules | CD45, 20, 22, 79a; bcl-6 | Good for stages I, II. Poor for advanced-stage disease |
| Nodular sclerosis | M = F, < 30 years with mediastinal mass, occasionally spleen or lung involvement. 40% have B symptoms. Most patients present with stage II disease | Broad bands of collagen, nodules of lymphoid tissue with 'lacunar cells' showing abundant pale cytoplasm. Classic HRS cells rare | CD15, 30 | Fair–good |
| Mixed cellularity | M > F, median age 37 years. Peripheral lymphadenopathy common, ± spleen, BM. B symptoms common. Patients often stage III or IV | Classic HRS cells with large, mono-, bi- or multinucleation, prominent nucleoli found in mixture of lymphocytes, plasma cells, eosinophils, histiocytes | CD15, 30 | Fair–good |
| Lymphocyte depletion | M > F, median age 37 years. May present as acute febrile illness with pancytopenia, BM, visceral organ involvement, B symptoms, advanced stage common. Associated with HIV | Classic HRS cells common with paucity of background lymphocytes. Pleomorphic HRS cells mimic a sarcoma | CD15, 30 | Fair–good stage for stage when compared to other CHL. HIV patients have more aggressive course |
| Lymphocyte rich classical | M > F, older age. Peripheral lymphadenopathy. B symptoms rare. Most patients with stage I or II disease | Scattered classic HRS cells among numerous small lymphocytes. Nodular growth pattern | CD15, 30 | Good |

L&H = lymphocyte and histiocytic; HRS = Hodgkin Reed–Sternberg; BM = bone marrow; CHL = classical Hodgkin lymphoma.

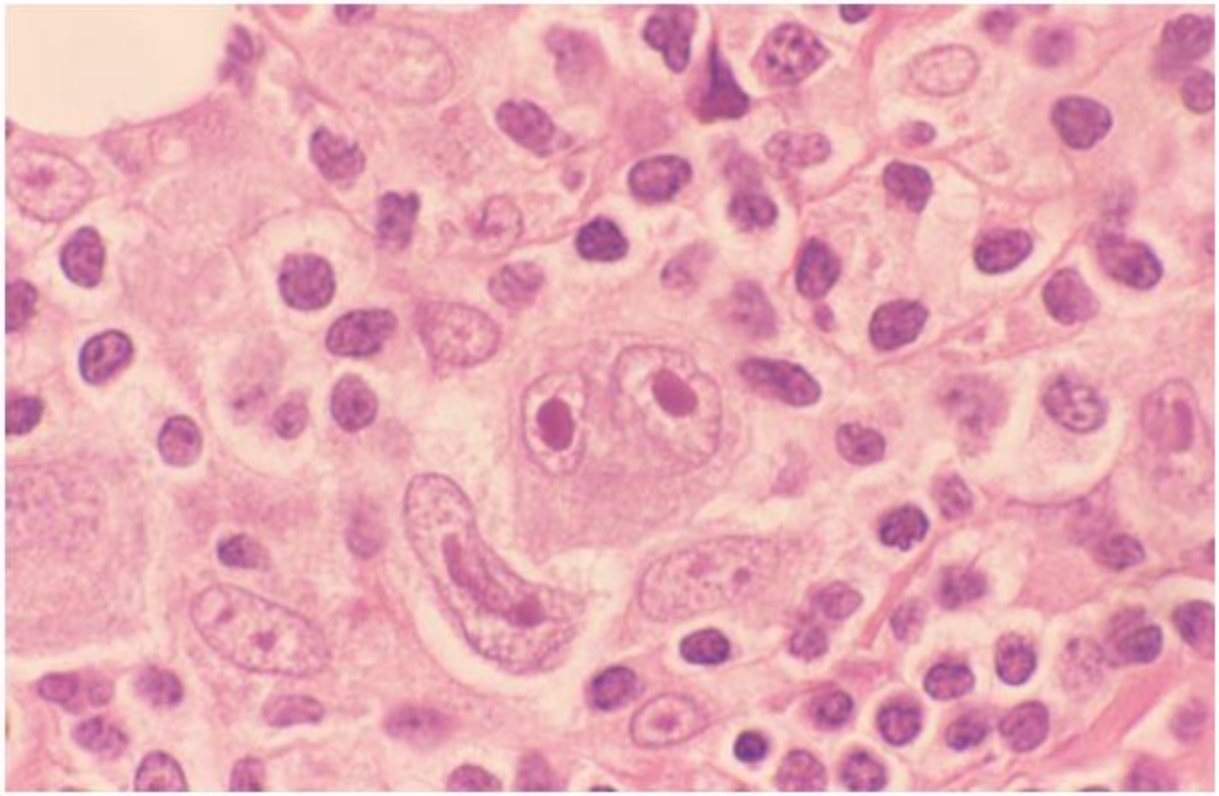


**Figure 17–7 Hodgkin's disease: Reed-Sternberg cell.** Large binucleate cell with prominent nucleoli in each nucleus.

*Table 19–1*

## Hematologic Effects of HIV

| |
|---|
| Anemia |
| Leukopenia |
| Thrombocytopenia |
| Dysplastic changes in the bone marrow |
| Antiphospholipid antibodies |
| Thrombotic microangiopathy |

(a) Stem cell transplantation. Harvested stem cells may be frozen and stored indefinitely. They may be 'processed', for example to concentrate CD34 cells or remove T cells. Procedures are available to 'purge' them of residual malignant cells (e.g. by use of monoclonal antibodies).

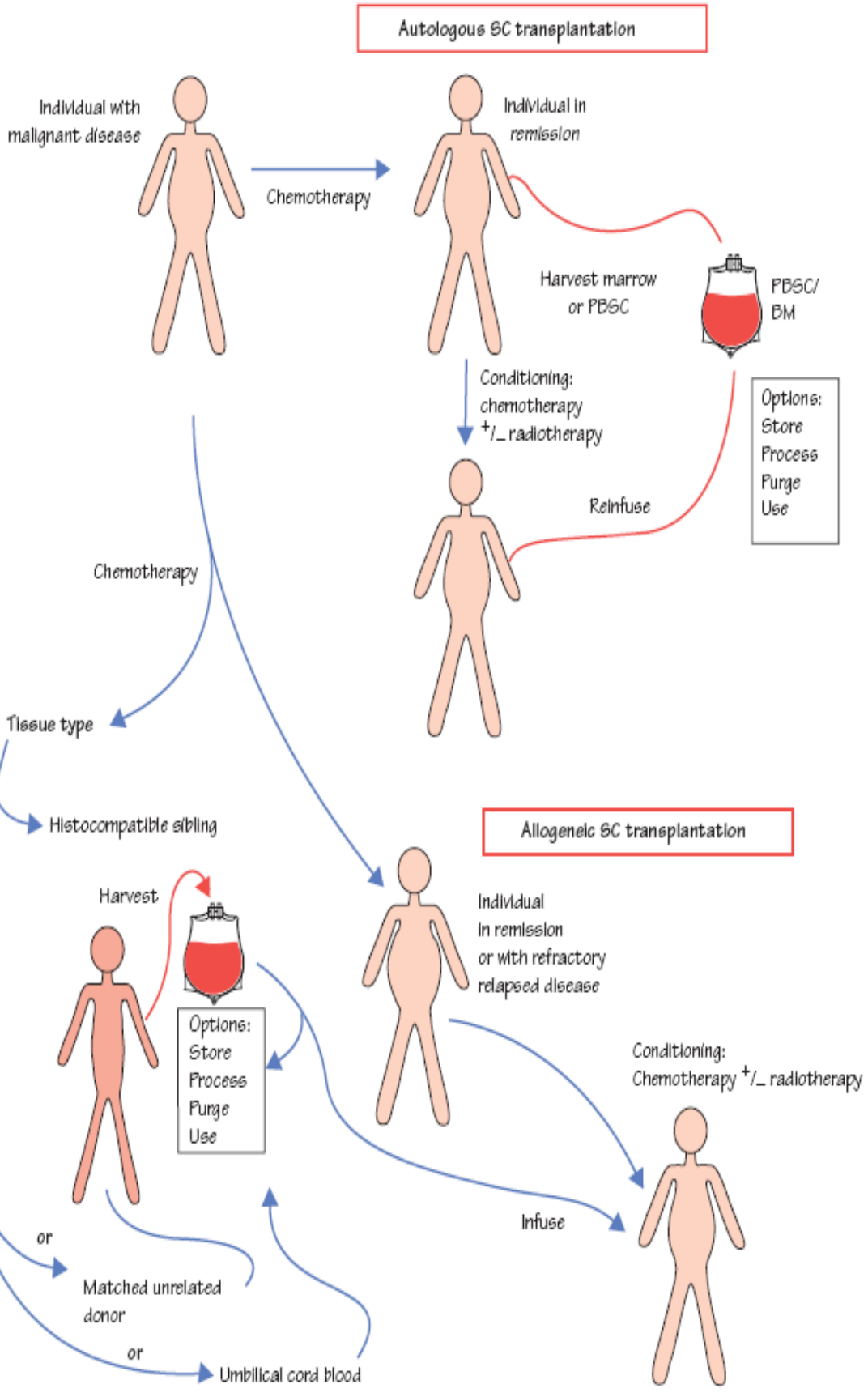


**Table 42.1** Indications for stem cell transplantation.

| Allogeneic | Autologous |
|---|---|
| Acute leukaemia | **Selected patients** |
| Standard/poor risk AML in first remission | Multiple myeloma |
| AML in second remission | Lymphoma |
| Poor risk childhood or adult ALL in first remission | Acute leukaemia |
| ALL in second remission | Autoimmune disease e.g. scleroderma |
| Chronic or accelerated phase CML | |
| Severe aplastic anaemia | |
| **Selected patients** | |
| Myelodysplasia | |
| Lymphoma | |
| Myeloma | |
| Chronic lymphocytic leukaemia | |
| Thalassaemia major, sickle cell disease | |
| Severe inherited metabolic diseases, e.g. adenosine deaminase deficiency, Hurler's syndrome | |

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia.

# Leukopoiesis and Leukopoietic Function

## *Summary Points*

- The myeloid:erythroid ratio (M:E) is 4:1.
- Segmented neutrophils are held in the marginating pool for 7 to 10 days before release to circulation.
- The white cell series in order of least mature to most mature is myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and segmented neutrophils.
- Cell identification is based on cell size, N:C ratio, presence or absence of granules, presence or absence of nucleoli, chromatin pattern, and texture of cytoplasm.
- The marginating pool designates those white cells located along the vessel endothelium.
- The circulating pool designates those white cells present in the bloodstream.
- Lymphocytes originate not only from the bone marrow but also from the thymus and the lymphatic system.
- The bone marrow and the thymus are the primary lymphoid organs.
- Spleen, lymph nodes, Peyer's patches, and the tonsils are the secondary lymphoid organs.
- The lymphatic system plays an important role in blood filtration, fluid balance, antibody generation, and lymphopoiesis.
- T cells represent 60% to 80% of the total lymphocyte count.
- B cells represent 10% to 20% of the total lymphocyte count.
- T helper and T cytotoxic/suppressor cells are essential in cell-mediated immunity.
- B cells support humoral immunity, which is antibody production by plasma cells.
- Absolute counts are derived from the total white counts multiplied by the relative percentage of a particular cell in the differential.

# Abnormalities of White Cells: Quantitative, Qualitative, and the Lipid Storage Diseases

## *Summary Points*

- Infections and inflammation will increase the number of neutrophils in the peripheral smear.
- Leukocytosis means an increase in white count.
- Eosinophils will be increased in skin diseases, parasitic infections, and transplant rejection.
- A left shift signifies that younger white cells will appear in the peripheral smear such as occasional metamyelocytes, many bands, and segmented neutrophils.
- Leukemoid reaction is an exaggerated response to infection or inflammation.
- In the leukoerythroblastic picture, young white cells, young red cells, and abnormal platelets will be seen.
- Phagocytosis is a process by which bacteria and other infectious agents are recognized and destroyed by neutrophils and monocytes.
- Toxic changes in white cells are observed as toxic granulation, toxic vacuolization, and Döhle bodies.
- Hereditary white cell disorders include May-Hegglin anomaly, Pelger-Huët anomaly, and Chediak-Higashi syndrome.
- Pelger-Huët anomaly is a hyposegmentation disorder in which the lobes of the segmented neutrophils are peanut shaped or bilobed.
- A hypersegmented nucleus, five lobes or more, is seen in megaloblastic disorders.
- Chediak-Higashi syndrome is a rare autosomal disorder of neutrophilic granules.
- Human ehrlichiosis represents a group of tick-borne diseases caused by *Rickettsia Ehrlichia chafeensis* and *Ehrlichia phagocytophilia*. Inclusions may be seen in the granulocytes and monocytes in the bone marrow.
- Reactive lymphocytes are lymphocytes transformed by viral infections or other disorders.
- Reactive lymphocytes are characterized by abundant basophilic cytoplasm, a lower N:C ratio, and clumped chromatin material.
- Infectious mononucleosis is caused by the Epstein-Barr virus, and patients show low-grade fever, sore throat, swollen glands, anorexia, and headache.
- Individuals with AIDS show a pancytopenia and a reversal in CD4 and CD8.
- Bacteria may appear intracellularly in neutrophils or may appear within the peripheral smear.
- Lipid storage diseases represent a group of inherited disorders in which a key metabolic enzyme is missing or inactive.
- Gaucher's disease and Niemann-Pick disease are lipid storage disorders showing large histiocytic-like cells in the bone marrow.

# Acute Leukemias

## *Summary Points*

- Leukemia is caused by the mutation of the bone marrow pluripotent stem cells.
- Individuals with acute leukemia will present with variable white counts, anemia, and platelet counts.
- When blasts cells accumulate in the bone marrow and peripheral smear, the leukemia is classified as acute.
- Hepatosplenomegaly or lymphadenopathy is more prominent in chronic leukemias than in acute leukemias.
- According to the WHO, the peripheral smear must contain 20% myeloblasts or greater for a diagnosis of acute leukemia.
- Skin infiltration is characteristic of monocytic leukemias; extramedullary hematopoiesis is common in monocytic or myelomonocytic leukemias.
- Headache, blindness, and other neurological complications are indicative of blast cells crossing the blood-brain barrier.
- Cytochemical staining can assist in the diagnosis of acute leukemias based on staining patterns.
- Auer rods are composed of fused primary granules and may be present in myeloblasts.
- Immunophenotyping can help to classify the clone of leukemic cells by using monoclonal antibodies in flow cytometry or immunohistochemistry procedures.

- Cytogenetic abnormalities such as translocation and deletion are an important prognostic feature of many acute leukemias.
- Acute promyelocytic leukemia is associated with disseminated intravascular coagulation.
- Treatment with cytotoxic chemotherapy and/or radiation therapy is associated with the develop ment of acute leukemia and myelodysplastic syn-drome.
- Acute myelocytic leukemia with maturation of the most common acute myelocytic leukemias.
- Acute lymphoblastic leukemia is the leukemia of childhood with highest incidence between the ages of 2 and 6 years.
- Acute lymphoblastic leukemia accounts for 76% of all leukemias diagnosed in children younger than 13 years.
- Children with Down syndrome have an increased risk of leukemia.
- Lymphoblasts will frequently cross the blood-brain barrier, causing neurological involvement.
- In the pediatric age group, children with acute lymphoblastic leukemia have an overall complete remission rate of close to 95%.

# Chronic Myeloproliferative Disorders

## *Summary Points*

- Chronic myeloproliferative disorders (CMPDs) are caused by abnormal stem cells that lead to unchecked autonomous proliferation of one or more cell lines.
- The most common CMPDs are chronic granulocytic leukemia, polycythemia vera (PV), myelofibrosis with myeloid metaplasia (MMM), and essential thrombocythemia (ET).
- The bone marrow in CMPDs may show hyperplasia or elements of fibrosis.
- Most of these disorders are seen in older adults and show a normochromic normocytic process.
- Individuals with chronic myelogenous leukemia (CML) show an extremely high white count, moderate anemia, and the entire spectrum of white cells in the peripheral smear.

- Ninety percent of CML individuals show the Philadelphia chromosome, which is a cytogenetic abnormality in which a small part of chromosome 9 is translocated to the broken arm of chromosome 22.
- A hybrid gene, *BCR-ABL,* is also manifested with Philadelphia chromosome, and this gene prevents natural cell death or apoptosis.
- In the accelerated phase of CML, a higher blast count may be present and eventually ends in blast crisis, all blasts in the bone marrow.
- PV is a clonal disorder of red cells in which the patient shows a pancytosis: high red count, high white count, and high platelet count.
- Patients with PV have symptoms related to hyperviscosity, including hypertension and vascular abnormalities.
- The leukocyte alkaline phosphatase score is usually elevated in PV and low in CML.
- Patients with PV must be distinguished from those with secondary or relative erythrocytosis.
- The major causes of death in patients with PV are hemorrhage and thrombosis.
- MMM is characterized by marrow fibrosis, extramedullary hematopoiesis, and the leukoerythroblastic blood smear.
- In patients with MMM, the accelerating fibrosis may contribute to leukopenia and thrombocytopenia.
- In 50% of patients with MMM, bone marrow aspirates are impossible because of increased fibrosis: the dry tap.
- MMM has the worst prognosis of all of the myeloproliferative disorders.
- ET is a clonal proliferation of megakaryocytes in the bone marrow.
- The peripheral count of patients with ET is extremely elevated, sometimes up to 1 million.
- The increased platelet count in ET can cause hemorrhagic and thrombotic episodes, including gastrointestinal bleeding, epistaxis, and transient ischemic attacks.
- Diagnosis for ET involves ruling out any other causes for reactive thrombocytosis other than the clonal proliferation of megakaryocytes.

# Lymphoproliferative Disorders and Related Plasma Cell Disorders

## *Summary Points*

- Lymphoproliferative disorders comprise the B and T lymphocytes in which there is a clonal malignant proliferation of either cell subset.
- Chronic lymphocytic leukemia (CLL) is a clonal proliferation of B lymphocytes that is seen in older patients and often discovered by accident.
- CLL shows an accumulation of mature lymphocytes in the bone marrow and eventually the lymph nodes, spleen, and peripheral blood.
- The white counts in CLL are extremely elevated and the M:E ratio is 10 to 20:1.
- Immune function is compromised in CLL, and 10% to 30% of individuals may experience autoimmune hemolytic anemia.
- Hairy cell leukemia (HCL) is a rare B-cell malignancy in which the cells have a lymphoid appearance but hair-like projections in the cytoplasm.
- Pancytopenia, splenomegaly, and dry tap are the key features of HCL.
- Sézary syndrome is the blood equivalent of cutaneous T-cell lymphoma that presents with a convoluted, cerebriform, ovoid nucleus.
- Multiple myeloma is a disorder of plasma cells that leads to a monoclonal gammopathy, bone involvement, and pancytopenia.
- Most of the abnormal proteins are an accumulation of IgG, which may lead to a hyperviscosity and rouleaux in the peripheral smear.
- Serum calcium is elevated in MM patients due to bone loss and increased distribution of calcium in the peripheral circulation.
- Bence-Jones protein may be seen in individuals with MM.
- Plasma cell leukemia is a complication of MM in which mature plasma cells are seen in increasing numbers in the peripheral circulation.
- Waldenstrom's macroglobulinemia is a rare disorder of plasma cells in which IgM is overproduced.
- Many of the symptoms of Waldenstrom's macroglobulinemia are related to hyperviscosity of the plasma, which accounts for coagulation abnormalities, rouleaux formation, and bleeding or thrombotic complications.
- Plasmapheresis, the therapeutic removal of plasma, may be used as a treatment to decrease the amount of abnormal IgM protein.

# The Myelodysplastic Syndromes

## *Summary Points*

- The myelodysplastic disorders (MDSs) are a group of clonal disorders characterized by refractory anemias and cytopenias of one or more cell lines.
- Dysgranulopoietic changes include abnormal granulation of mature cells, hypersegmentation, hyposegmentation, or complete lack of granulation.
- Dysthrombopoietic changes include micro-

changes, nuclear bridging, macrocytes, and dimorphism.

- The bone marrow and peripheral smear will show dysplastic changes in white cells, red cells, and platelets over time.
- Dyserythropoietic changes include multinuclear red cell precursors, bizarre nuclear

megakaryocytes, abnormal granulation, no granulation, and giant platelets.

- The blast count in the MDS is less than 20%.
- Weakness, infections, and easy bruising are some of the symptoms that patients with MDS may manifest.
- According to the World Health Organization, there are six classifications of MDSs.

پایان